TOFIQ Journal of Medical Sciences
ISSN: 2377-2808

Tofiq Journal of Medical Sciences (TJMS)

Vol.(1).No.1 ,2014

ISSN: 2377- 2808

www.tofiq.org

TOFIQ Journal of Medical Sciences
ISSN: 2377-2808

TOFIQ Journal of Medical Sciences

TOFIQ Journal of Medical Sciences (TJMS) is published by TOFIQ: an NGO registered at the State of Maryland as a non-profit organization dedicated to helping Iraq Higher Education and Research.

TJMS is devoted to the publication of original research, commentaries on a current topic, reviews, letters to the editor, and editorials in the field of medical sciences. The early focus of the journal is on clinical burden of disease in Iraq: documentation of its nature and extent; clinical patterns and epidemiology; diagnostic findings; and therapeutic strategies.

ANNOUNCEMENT

Invitation to authors

We invite all members of the Iraqi American Academic Community to contribute to this first issue with: Reviews, Commentaries on a current topic, or Letters to the editor. They may submit directly on the TJMS site or send it by email to the Editor's address in "Journal Contact".

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Letter from Editor–in- Chief

Dear Colleagues,

On behalf of the editorial board of TOFIQ Journal of Medical Sciences, TJMS, it is my privilege to announce the establishment of this new Medical Sciences Journal.

TJMS is an international, peer-reviewed open access online journal published by TOFIQ, which is a non-governmental non-profit NGO established by Iraqi American academics and professionals in the United States of America.

TJMS is devoted to the publication of original research, commentaries on a current topic, reviews, letters to the editor, and editorials in the field of medical and related sciences.

The early focus of the journal is on clinical burden of disease in Iraq: documentation of its nature and extent; clinical patterns and epidemiology; diagnostic findings; and therapeutic strategies.

We invite submission of articles on topics pertaining to the science and art of medicine that help fulfill the journal's mission of publishing information in medicine, dentistry, pharmacy, nursing, bioengineering and all related sciences that can be used by scientists, clinicians and professionals in the medical fields to improve patient care and public health.

Our main aim is to help our Iraqi researchers to have their scientific voice heard all over the world.

I look forward to your support for your submission to TJMS.

With best regards,

A Hadi Al Khalili, MB ChB, FACS, FRCSE, MPhil

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TOFIQ Journal of Medical Sciences
ISSN: 2377-2808

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ISSN: 2377-2808

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ISSN: 2377-2808

2014

Vol 1, No 1 (2014)

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ISSN: 2377-2808

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THE CHANGES IN THE INCIDENCE OF GASTRIC VERSUS COLORECTAL CANCER IN IRAQ DURING THE PERIOD BETWEEN 1965-2006

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Abstract

Background:

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death in the world, while the colorectal cancer (CC) is the third commonest cancer in US and second most common in Europe.

Objective:

This study is aiming to identify the incidence of both GC and CC and their stages in Iraq over a period of forty two years.

Methods:

A retrospective audit study of 2240 cases with 1237 patients with GC and 1003 patients with CC were operated on between 1965-2006 included. The age, sex, stage and the incidence of each cancer every two years for the study period were reported and compared with the Iraqi Cancer Registry and the published data.

Results:

Gastric cancer affected males more than females. The average age for GC was 53.66 for males and 50.47 year for females. The average age for CC was 56.83 year for males and 53.65 year for females. The GC counted for around 2/3 of cases in the cases in the late sixties, while in the early eighties the CC constituted around 3/4 of the total number of cases assessed in this diagnosis. There was a significant increase in earlier cancer stages for both cancers in the later half of the study period. Comparing the first half to the second half with the second one, we found an insignificant rise in the number of cases of GC while there was a significant increase number of CC comparing both periods.

Conclusion:

There was a change in the pattern of gastrointestinal cancer, particularly GC and CC in Iraq, which was attributed to dietary factors. On the other side there was a significant increase number of early staging cancer. These findings mimic the Iraqi Cancer Registry and the western results.

Introduction:

Gastric cancer (GC) is fourth most common cancer in the world with just under one million cases recorded in the year 2008, behind cancers of the lung, breast and colorectal, respectively. It is also the second leading cause of cancer death in both sexes worldwide.

(1) In Iraq, it is the leading gastrointestinal malignancy (2,3) while colorectal cancer (CC) was the third after the oesophagus (3, 4). Gastric cancer include any malignant tumor (excluding gastrointestinal stromal tumours) arising from the region extending from the gastroesophageal junction (GOJ) and the pylorus, it may not be possible determine the site of origin if the cancer involve the GOJ itself; a situation that has become more common in recent years, especially with the rising incidence of Barrett's and its related GOJ cancers. The majority of Gastric Cancers are adenocarcinoma, almost two thirds of them occur in developing countries with peak incidence in the far east regions including China, Korea and Japan.

Colorectal cancer is the third commonest cancer in USA following prostate and lung/bronchus cancer (5) and the second commonest cancer in Europe following breast cancer (6). The incidence of CC incidence in Iraq was increasing gradually within the last three decades (8). The risk of developing CC begin to increase at age 40 years and rises with age (8). Screening for colorectal cancer reduced the number of cases with late stages and increased those with early stage cancer (9).

Aim:

The aim of this study is to present the changes noticed in the rise of CC versus the GC in Iraq during the period (1965-2006), especially in the last three decades of the past century.

THE CHANGES IN THE INCIDENCE OF GASTRIC VERSUS COLORECTAL CANCER IN IRAQ DURING THE PERIOD BETWEEN 1965-2006

Patients and Methods:

A retrospective audit study on 2240 cases, 1237 patients with GC and 1003 patients with CC operated upon by the senior surgeon (Al-Bahrani ZR) at the medical city University hospital and Al-Mustansiria private hospital, Baghdad from 1965-2006, included. The majority of both cancers were adenocarcinoma.

The age, sex, stage and the incidence of each cancer every two years for the study period were reported. The stage of GC and CC were recorded according to American Joint Committee on Cancer (AJCC). (10) We divided the total number of cases between two groups of twenty one years each; period A 1965-1985 and period B 1986-2006. The stages of each cancer were compared between different the two periods. The results were compared between both cancers and with the reports from the Iraqi Cancer Registry.

Results:

Adenocarcinoma of the stomach constituted 90% of all gastric cancers (1117 out of 1237 cases), the rest of the cancers were malignant lymphoma (120 cases, 10%). Gastric cancer affects males more than females with a reducing male: female ratio of 2.3:1 in 1971 to 1.6:1 in 2006. The peak age incidence for GC was in the fifth decade for women while it was in the sixth decade for men. (Figure 1) The average age for GC was 53.66 for males and 50.47 year for females. The males exceeded the females at all age groups except in patients less than 25 years old where the incidence of GC was higher in females than males.

Almost all colorectal cancers were adenocarcinoma (985 cases, 98%); there were only 18 (2%) cases with malignant lymphoma. The same male: female distribution and same age incidence occur for CC with one exception that the incidence of males was higher than females in all age groups. (Figure 2) The average age for CC was 56.83 year for males and 53.65 year for females. It was also noticed that the difference between males and females was minimal (2-5 patients per decade) at age of 54 years and below in CC. In both cancers, the incidence dropped steadily after their peeks in both sexes.

The GC counted for around 2/3 of cases in the cases in the late sixties and continue to increase until reach the peak of around 84% in 1971/1972 where the colorectal reach the lowest incidence of 16% of cases in that period. Then the percentage of both cancers reversed to the original 2/3 for GC and 1/3 for CC by the late seventies where it remained around that figure until mid nineties where the number of CC reach almost same

percentage of GC. After that there were persistent increase in the incidence of CC with continue drop in the percentage of GC until the end of the study period where CC consume 3/4 of cases versus 1/4 for GC in the year 2005/2006. Actually, the number of GC had not dropped that much but the number of CC had increased significantly to reverse the percentage ratio of the total number of cases on that period. (Figure 3)

Comparing the two period groups, we found there was slight increase in the total number of GC from 539 cases in period A to 689 cases in period B, which is statistically insignificant. On contrary, there was a statistically significant increase (over three fold) in the number of cases of CC between the two periods; from 241 cases in period A to 762 cases in period B.

Comparing the stage of each cancer between the two periods, there was an increase in stage I and II and drop in stage IV for GC from period A to period B; this was statistically significant for stage I and a trend toward significance for both stage II and IV. There was no much change in stage III between the two periods. (Table 1)

For CC, there was significant increase from period A to period B for stages II and III, while a significant drop in stage IV was demonstrated in period B compared with period A. (Table 2)

Comparing stage I and II together and stage III and IV together for both cancers during the two periods, there was significant increase in cases with stage I and II (*p:* 0.006) and significant drop in stage III and IV (*p:* 0.006) in the period B versus period A for GC. Similar changes found between both periods in CC but with a trend toward significance for both staging groups (*p:* 0.052). (Table 3)

Discussion:

There was a statistical significant drop in the GC incidence in the USA in the period between 1975-2004 (11). A similar drop was noticed in areas outside the USA (12), even noticed in higher risk countries at the far east of Asia (13). Such drop was reported by the Iraqi Cancer Registry (3) over the periods between 1976-2000; from 3.98% in 1976-1985 to 3.58% of the TBC in 1998-2000 (Table 4) and lately the incidence of GC was reported by AlHasnawi *et al* (7) with further drop to 3.3% of the TBC. A similar drop was found in our report. There is strong evidence for an association between environment and diet with GC. Studies of immigrants have shown that high risk population for GC from Japan or Korea has a dramatic decrease in the risk of GC when migrate to the west and change their dietary habits (8). The essential steps for prevention and control strategy for gastric

malignancy would be focus on control Helicobacter pylori, healthy diet, anti-tobacco campaign, early detection and diagnosis and treatment program (14).

Gastric cancer Affect men more than women with a ratio of male/female about 1.7:1 (8), while in Iraq, we reported a ratio of 2.3 /1 in 1971 (2) and here we reporting a drop up to 1.6/1 in the year 2006. Gastric cancer prevalence increases with advancing age with the peak in the seventh decade of life (8) while in our study; the peak is in the sixth decade in the males and in the fifth decade in females. (Figure 1)

The availability of the endoscopy units with easy access for both national health and private sectors led to early diagnosis and drop in the cancer staging for GC. We reported a significant increase in earlier stages (stage I and II) of GC in the second two decades of the study. (Table 1 and 3)

Colo-rectal cancer is a major problem in western countries, ranked the third cause of death from cancer in both sexes. The environmental, nutritional, genetic and familial factors, in addition to pre-existing disease have been found to be associated with colorectal cancer. Aspirin and Celecoxib (15) appear to decrease the risk of colorectal cancer in those at high risk. Vitamin D, dietary calcium supplement and proper nutrition are important factors in reducing colorectal cancer risk and colorectal adenoma (16-19). We believe that several factors shared causing this rise of CC in Iraq, including Kurdistan region, with change pattern toward western life.

In Iraq, excluding the three Northern provinces (Sulaimanyia, Erbil and Dohouk), CC is the seventh commonest cancer following breast, lung/bronchus, leukaemia, bladder, brain/CNS and lymphoma in the period between 2000-2004 (7). There was an increase incidence of CC over the last three decades from 3.39% of the total body cancer (TBC) in 1976-1985 to 4.6% in 1998-2000. (3) There was a slight drop in CC incidence in the years between 200-2004 to 4.2% of the TBC. (Table 4) This may be due to the Iraq invasion, The Third Gulf War, in 2003 where there was a drop in the registered cancers to the ministry of health. In the Northern Iraq, Kurdistan Region, CC was the fifth commonest cancer in 2009 following leukaemia, breast, lymphoma and lung/bronchus. (20). We reported a constant increase in the number of CC over the last two decades reaching the peak in 2006 (Figure 3). Our findings of the change in the incidence of colorectal versus the gastric cancer was also reported by the data reported by the six Iraqi reports illustrated in Table 3 and by AlHasnawi 2009 *et al* (7).

In Colorectal cancer the mean age at presentation is 60-65 years (2). In our review, the peak incidence occurs at earlier age group; sixth decade in males and the fifth decade in females. (Figure 2)

Type of food, stress of work to both sex, smoking, use of frozen food and appearance of inflammatory bowel disease especially ulcerative colitis in the second half of last century (21) while it was rare before. Diagnostic tools, increase number of specialists trained gastroenterologist after opening several specialized centers in the country and use of flexible scopes, the awareness of the early symptoms of colonic cancer lead to the early diagnosis in the last two decades of the last centaury, on contrary to the silent and late symptom and sign of gastric neoplasm. As a result, there was an increase in number of cases and early diagnosis of CC over the last two decades compared to the first two decades of this study group of patients.

Three main screening tests are available that aided early diagnosis; faecal occult blood testing, flexible Sigmoidoscopy and colonoscopy. These tests became a widely spread and available to the public through the National Health screening programs and public awareness. Screening endoscopy reduced the risk of late stage CC diagnosis, while people lives in rural area with less education and screening facilities associated with increased rate of late stage diagnosis (9). Similar to GC, there was a drop in the late stages of the CC in the period B with trend toward significance. (Table 3) This could be related to the availability of endoscopic units and the education of the general population about symptoms related to CC.

A new screening test is m2-pk test. Tumor pyruvate kinase M2 (tumor M2-PK) is a key enzyme in the altered metabolism of tumor tissue. Tumor M2-PK is elevated in a range of gastrointestinal malignancy, among these is CC (22). It was recommended through a recent meta-analysis that a stool tumour M2-PK to be used as a routine test for CC screening. It closes a gap in clinical practice because it detects bleeding and non-bleeding tumors and adenoma with high sensitivity and specificity (23). We need to introduce these tests in Iraq, including Kurdistan, to improve the early stage diagnosis of CC, in addition to other screening methods.

In conclusion, There is a reduction in the rate of GC and increase that of CC in Iraq over the last two decades of last centaury. This change could be related to westernized diet, stress and the early diagnosis with the availability of endoscopy. The last had led to early diagnosis and significant drop in the stage of both GC and CC.

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Figure 1: Age distribution for Gastric Cancer (1965-2006)

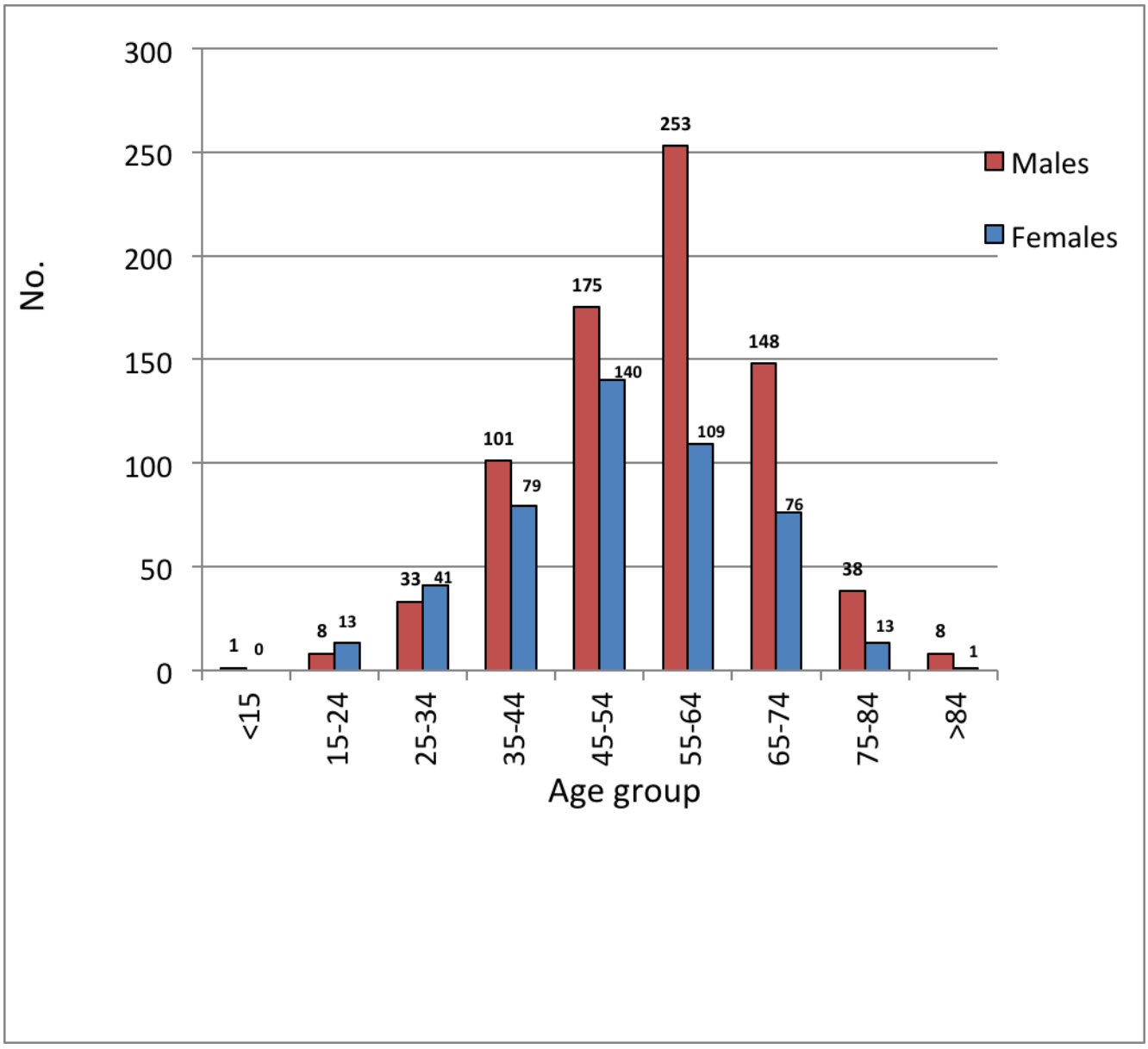

Fig. 1

Figure 2: Age distribution for Colorectal Cancer (1965-2006)

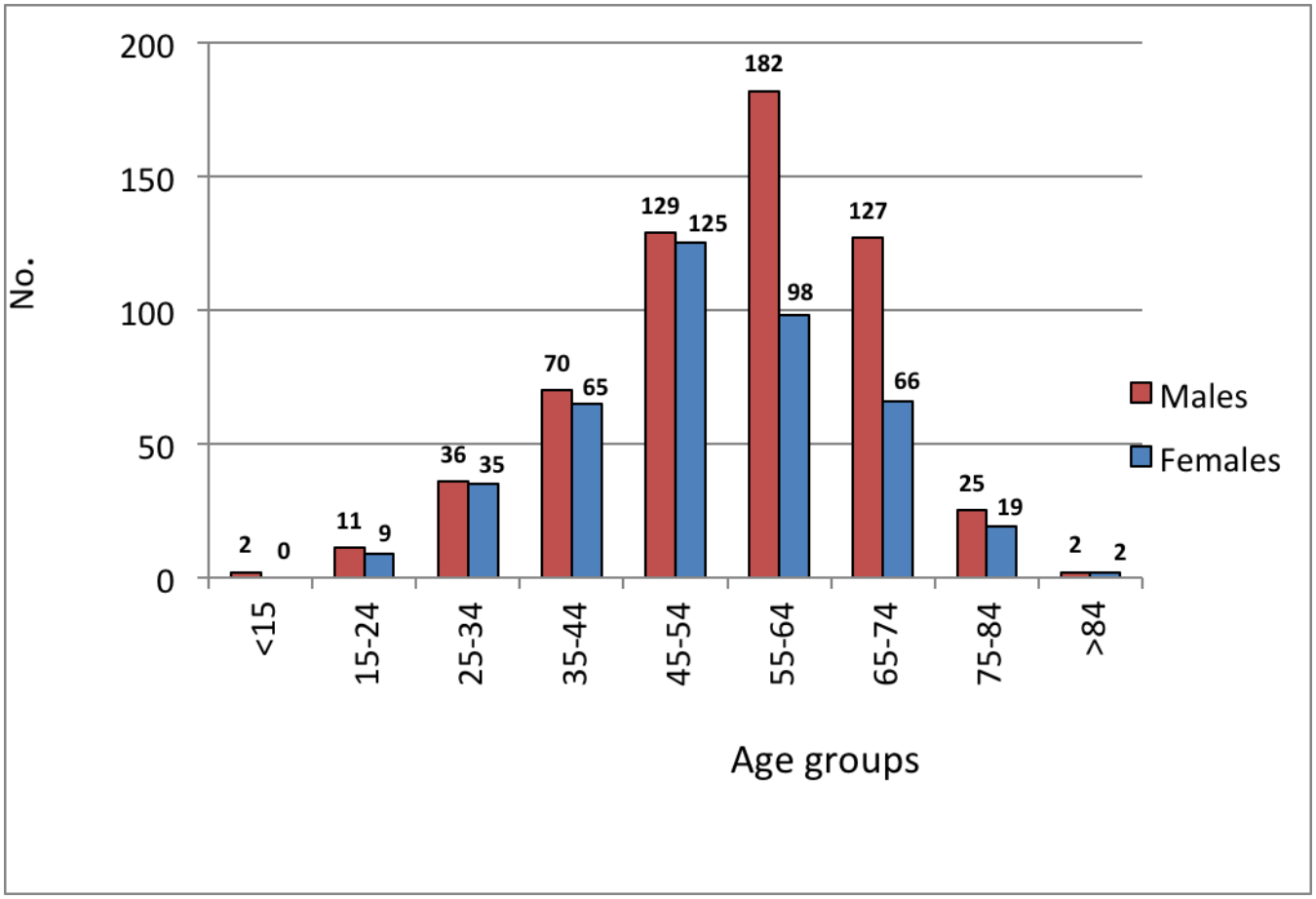

Figure 3: Percentage of gastric and colorectal cancer out of the sum of both cancers (1965-2006)

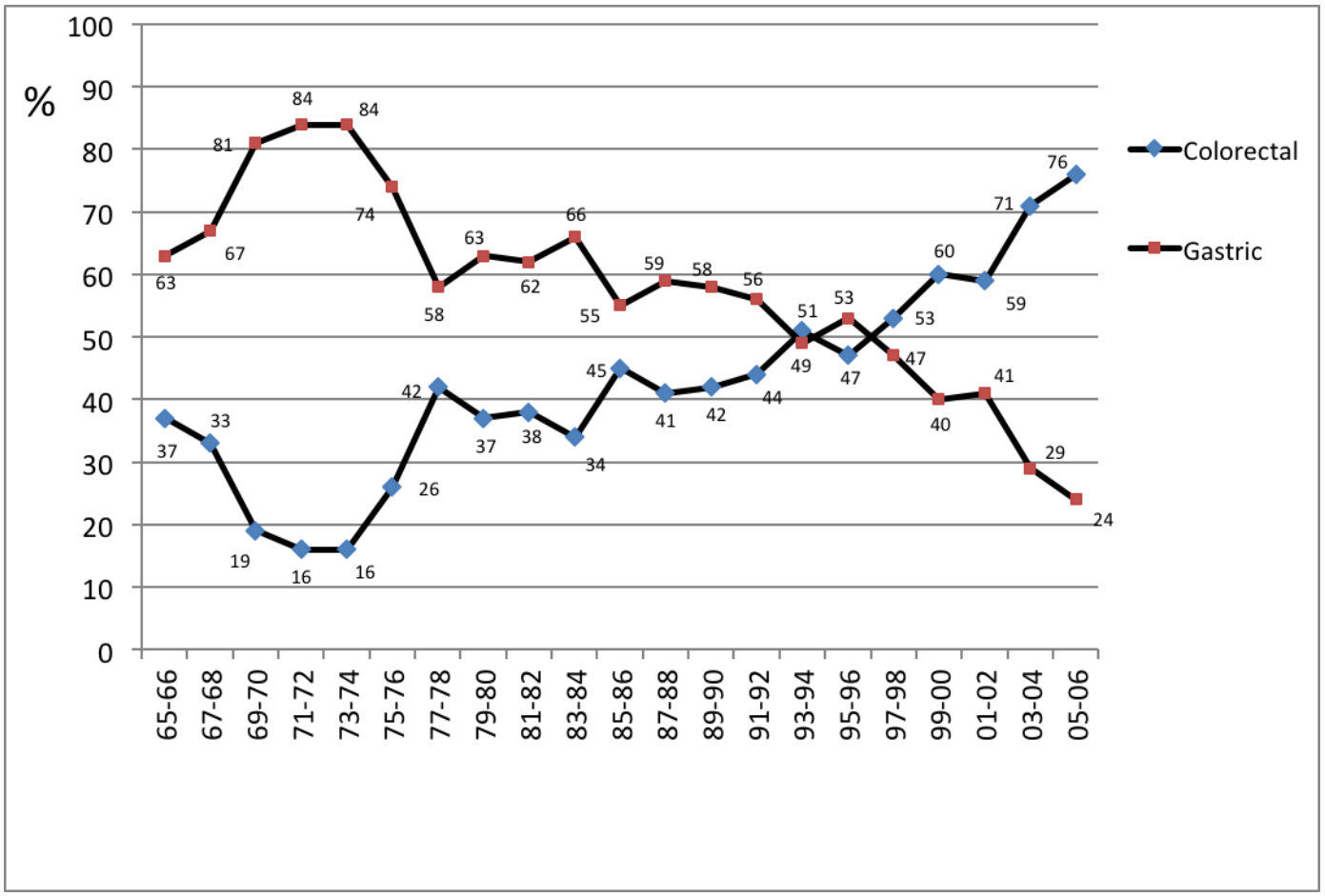

Table 1: Gastric Cancer staging compared between two periods

Stage	Period A (1965-1985)		Period B (1986-2006)		*p value*
	No	%	No	%	
I	1	0.2	14	2	0.004*
II	41	7.6	74	10.6	0.072**
III	168	31.2	222	31.8	0.811***
IV	329	61.0	388	55.6	0.052**
Total	539	100	698	100	

No: number

*: Statistically significant

**: Trend toward statistical significance

***: Not statistically significant

Table 2: Colorectal Cancer staging compared between two periods

Stage	Period A (1965-1985)		Period B (1986-2006)		*p value*
	No	%	No	%	
I	21	8.7	68	8.9	0.920*
II	58	24.1	235	30.8	0.044**
III	65	27.0	270	35.4	0.015**
IV	97	40.2	189	24.8	<0.001**
Total	241	100	762	100	

No: number

*: Not statistically significant

**: Statistically significant

Table 3: Staging groups for both cancers during the two periods

Site	Stage	Period A (1965-1985)		Period B (1986-2006)		*p value*
		No	%	No	%	
GC	I + II	42	8	88	13	0.006*
	III + IV	497	92	610	87	0.006*
CC	I + II	79	33	303	40	0.052**
	III + IV	162	67	459	60	0.052**

GC: Gastric Cancer, CC: Colorectal Cancer, No: number

*: Statistically significant

**: Trend toward statistical significance

Table 4: Percentage of Gastric vs. Colorectal cancers out of total body cancers between 1976-2000

Percent of Gastric & Colorectal Cancer
out of total body cancer in IRAQ (1976-2000)

Years of report *	Gastric	Colorectal
1976 – 1985	3.98	3.39
1986 – 1988	4.1	3.8
1989 – 1991	3.2	3.9
1992 – 1994	3.8	4.1
1995 – 1997	3.2	4.0
1998 - 2000	3.58	4.64

* Report of Iraqi Cancer Registry (Ministry of Health)

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THE USE OF ATORVASTATIN IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND IT'S EFFECTS ON THE DISEASE ACTIVITY AND ACUTE PHASE REACTANTS

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Key Words: Rheumatoid Arthritis, disease activity index, atorvastatin

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Abstract

Background

Rheumatoid arthritis (RA) is a common chronic inflammatory disorder characterized by synovitis, articular destruction, and many systemic extra-articular features**.** It is associated with a high rate of morbidity and mortality due to accelerated atherosclerosis and increased cardiovascular risk. Atorvastatin is a well-known anti dyslipidemic agent that might have valuable anti-inflammatory and immune modulatory functions in RA.

Objectives

The present study was performed to evaluate the anti-inflammatory effect of atorvastatin when used as adjuvant therapy to methotrexate (MTX) and etanercept in Iraqi patients with moderate to highly active RA.

Patients and Methods

A double blind randomized placebo - controlled clinical trial in which 100 patients, both males and females were included. All cases were with active RA who were on MTX and etanercept for at least one month. The cases were divided into two groups to receive either 20 mg atorvastatin or a placebo capsule for three consecutive months. Only 49 patients completed the three months trial, (25 in atorvastatin and 24 in placebo group).

All patients were clinically evaluated by measuring swollen joint count (SJC), tender joint count (TJC), visual analogue scale (VAS) and disease activity score (DAS28).Blood samples of RA patients were evaluated for erythrocyte sedimentation rate (ESR), C reactive protein (CRP) at baseline, monthly and at the end of the study.

Results

RA patients receiving 20mg atorvastatin showed a significant ($p<0.05$) reduction in CRP, SJC and TJC compared to those on placebo. In addition, atorvastatin helped to reduce ESR, VAS and DAS28 more than placebo but without achieving statistical significance ($p>0.05$).

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Conclusions

Atorvastatin 20mg is a safe and well-tolerated drug that has a modest anti-inflammatory effect in patients with moderate to highly active RA.

THE USE OF ATORVASTATIN IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND IT'S EFFECTS ON THE DISEASE ACTIVITY AND ACUTE PHASE REACTANTS

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Background

Rheumatoid arthritis (RA) is a common chronic inflammatory disorder characterized by synovitis, articular destruction, and many systemic extra-articular features[1]. It usually presents with pain, swelling and stiffness affecting the small joints of the hands, feet and wrists[2]. The onset of disease can occur at any age, but the peak incidence occurs within the fourth and fifth decades of life. The average annual incidence of RA in the United States is 0.5 per 1000 persons per year [3]. It is associated with a high rate of morbidity and mortality due to accelerated atherosclerosis and increased cardiovascular risk [4]. Atorvastatin is well known anti dyslipidemic agent that mediates clinically significant cardiovascular risk reduction in patients without inflammatory disease by inhibiting 5-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme. It has been found that atorvastatin can exert an anti-inflammatory effect in addition to its lipid-lowering actions in animal studies through inhibition of neutrophil infiltration and the local production of pro-inflammatory cytokines (tumor necrosis factor-a (TNF-α),interleukin-1 (IL-1) and interleukin-6 (IL-6)) and chemokines (CCL2 and CCL5) which significantly decrease tissue destruction [5]. Many clinical trials include usage of atorvastatin in rheumatoid arthritis patients as adjuvant therapy to disease modifying

anti-rheumatic drugs (DMARDs), but most of these trials were performed on stable RA patients rather than those with active arthritis [6,7,8].

The present study was performed to evaluate the anti-inflammatory effect of atorvastatin when used as adjuvant therapy to methotrexate and etanercept in a group of Iraqi patients with moderate to highly active RA.

Patients and Methods

Study design

This was a 13-week randomized double blind placebo-controlled single center trial conducted at Rheumatology Unit, Baghdad Teaching Hospital, Baghdad, Iraq from 1st November 2012 until 1st June 2013. One hundred patients of both genders with active RA, who were on MTX and etanercept for at least one month, were divided into two groups to receive 20 mg atorvastatin tablet previously grinded and filled in capsules or capsules prefilled with starch as placebo orally for three consecutive months. The capsules were prepared and packed by a pharmacist who kept a log-book of the coding. The researchers had no way to know the content of the capsules.

Atorvastatin was bought from Micro Company, India under trade name (Avas® 20mg). Patients were evaluated at baseline, monthly and at week 12.

Sample selection

Eligible patients had confirmed RA according to the 1987 American College of Rheumatology (ACR) criteria [12] with moderate to highly active disease defined as disease activity score based on 28 joints and ESR

(DAS28-ESR) greater than 3.2 at baseline. For inclusion, patients also were required to have taken methotrexate (MTX) and etanercept regularly for at least one month. The exclusion criteria included patients who were taking lipid-lowering therapy, had hypersensitivity to statin, pregnancy, breast feeding, renal and liver impairment and patients younger than 18 years old.

Informed consent was obtained from all participants and the ethical committee of Baghdad University, College of Medicine – Medical Department, approved this study.

Clinical and laboratory evaluation

Clinical evaluation of patients for tender and swollen joints was done by a specialized rheumatologist who was blinded to the treatment at the beginning, monthly and after 12 weeks of treatment. The RA disease activity was measured using DAS28-ESR, which is a validated composite [9] and was calculated by the following equation:

$$\mathbf{DAS28 = 0.56\ (TJC)^{0.5} + 0.28(SJC)^{0.5} + 0.70 \ln (ESR) + 0.014(VAS)}$$

-TJC, tender joint count

-SJC, swollen joint counts

-ESR, erythrocyte sedimentation rate

-VAS, visual analogue scale

Blood specimens were collected and laboratory analyzed (at baseline, monthly and after 12 weeks) for the measurement of ESR and CRP. ESR was measured by Westergren method [10] while C-RP was measured by slide agglutination test [11].

Statistical analysis

Statistical software (SPSS version 20) was used for data input and analysis. Continuous variables were presented as mean ± standard deviation (SD) and discrete variables were presented as numbers and frequencies. Chi square test for independence was used to test the significance of association between discrete variables. Continuous variables were tested by the Shapiro Wilk test to determine if they were normally or abnormally distributed. Mann Whitney test was performed to test the significance of difference in the mean of two samples in abnormally distributed continuous variables. Findings with P value less than 0.05 were considered significant whereas P values less than 0.01 considered highly significant.

Results

In this randomized double blind study, 100 patients were included in the study and randomly assigned to receive atorvastatin or placebo. Half of them received atorvastatin and the other half received placebo. Ten patients in the atorvastatin group and five patients in the placebo group withdrew within the first month of the trial and those patients were excluded from the study. Twenty five patients in the atorvastatin group and 26 of patients in the placebo group did not complete the three month treatment course. Patients in the two groups had similar demographic and baseline characteristics. Patients were predominantly middle-aged women (80.25% of the atorvastatin group vs 80% of controls) with disease duration more than eight years . Most of them have positive rheumatoid factor (57.5% of the atorvastatin group vs 68.9% of controls) . C-RP is nearly similar between the two groups . Most of the patients in the two groups are non smokers 87.5% of the atorvastatin group vs 88.9% of controls)). Table 1 shows the mean value of the indices used to evaluate the progress of the patients in the two study groups. It shows a significant difference at pre-treatment ESR level between atorvastatin and placebo group ($p=0.017$). There was a progressive and highly significant decrease in ESR level in atorvastatin groups during the first, second and third month of treatment compared to pre-treatment level. While in the placebo group, the only significant decrease in ESR level was seen after completing three months of treatment.

However, there was no significant difference ($p=0.58$) between the ESR levels of the atorvastatin and placebo at the end of the study.

The CRP levels for patients taking atorvastatin was significantly lower compared to patients receiving placebo after one month of treatment ($p=0.008$).

The SJC of patients receiving atorvastatin for three months was significantly lower compared to patients receiving placebo ($p=0.028$).

The TJC in patients receiving atorvastatin was significantly lower compared to patients receiving placebo after two months of treatment ($p=0.041$).

There was a non-significant difference (p=0.115) in the VAS between the atorvastatin and placebo groups during three months of treatment.

A non-significant difference (p=0.23) in DAS28 between the atorvastatin and placebo groups during three months of treatment.

Table 1 Mean ± s.d. of Indices Used in the Effect of atorvastatin and placebo Groups

Test	Group	Pre treatment	After treatment for		
			1 month	2 months	3 months
ESR	Atorvastatin	58.35±22.9 (n=40) ♣	41.88±20.33 (n=40) **	37.18±20.41 (n=28) **	35±17.18 (n=25) **
	Placebo	48.69±29.75 (n=45)	44.38±25.37 (n=45)	40.42±23.25 (n=33)	33.17±18.0 (n=24) *
CPR	Atorvastatin	38.8±20.17 (n=40)	23.55±16.77 (n=40) **♣	17.79±13 (n=28) **	13.2±6 (n=25) **
	Placebo	40.8±30.74 (n=45)	33.42±28.37 (n=45) *	22.91±14.73 (n=33) *	16.75±11.73 (n=24) *
SJC	Atorvastatin	4.95±4.26 (n=40)	3.13±3.87 (n=40) **	2.25±2.048 (n=28) **	1.6±1.58 (n=25) **♣
	Placebo	5.31±4.15 (n=45)	4.02±3.65 (n=45) *	3.64±3.35 (n=33) *	2.96±2.47 (n=24) *
TJC	Atorvastatin	8.68±5.27 (n=40)	5.43±4.34 (n=40) **	3.5±3.54 (n=28) **♣	2.68±2.41 (n=25) **
	Placebo	6.87±5.26 (n=45)	5.98±5.09 (n=45)	5.36±3.77 (n=33)	4.33±2.94 (n=24)
VAS	Atorvastatin	6.63±1.9 (n=40)	4.93±1.91 (n=40) **	4.25±1.91 (n=28) **	3.6±1.47 (n=25) **
	placebo	6.04±1.93 (n=45)	5.16±1.87 (n=45) **	4.94±2.13 (n=33) **	4.29±1.78 (n=24) **
DAS 28	Atorvastatin	5.80±1.07 (n=40)	4.70±1.16 (n=40) **	4.23±1.15 (n=28) **	3.95±1.01 (n=25) **
	placebo	5.33±1.17 (n=45)	4.91±1.33 (n=45) *	4.77±1.10 (n=33) *	4.43±1.04 (n=24) *

Note: values shown as mean± standard deviation , ***** significantly different compared to pretreatment within the same group ($p<0.05$);****** highly significant difference compared

to pre treatment within the same group (P<0.01), ♣ significant difference of the effect of atorvastatin compared to placebo within same month (P<0.05).

Discussion

This study was designed as a double blind randomized clinical trial, which is compatible with a high rate of agreement and decreases the possibility of bias [13]. Because it is ethically unaccepted to use atorvastatin alone as a separate arm in the trial, adjuvant therapy to methotrexate and etanercept pattern is implemented. Moreover, atorvastatin was not compared alone versus placebo to avoid the unacceptable risks in patients who remain untreated for the required duration of the trial [14].

A high dropout rate was observed in the present study in patients randomized to atorvastatin or placebo but there was non-significant difference between the two treatment groups in this aspect. In the country of Iraq, where the security situation is still volatile, and patient education is low, it is always expected to have a high dropout rate with an impossible task of tracing the patients.

Only 49% of patients completed the three month trial. The other non-completers showed no evidence for the reasons of withdrawal. However , withdrawal may be due to poor compliance , adverse effects of treatment , lack of efficacy , cultural factors or other reasons.

Acute phase reactants ESR and CRP provide reliable means for discrimination between drugs that provide symptomatic relief only and others with a more profound effect in RA [15].

The ESR is sensitive for most types of inflammation, but cannot distinguish if the underlying cause is infectious, inflammatory, or paraneoplastic [16]. The results of this study showed that ESR level in RA patients with active disease was significantly reduced by using 20mg atorvastatin (but less in placebo) over three months of treatment, but with no significant difference between atorvastatin and placebo at the end of the study. Similar result was found in a trial using 80mg atorvastatin for 12 weeks versus placebo [17]. The

same finding was reported when 10mg rusovastatin was used for 38 patients for 8 weeks [18]. Many other studies showed that atorvastatin has the ability to reduce ESR significantly when compared to placebo [19-21]. The different results of those trials from the present findings may be attributed to that this study use 20mg atorvastatin in contrast to 40mg used in other studies. In addition, this study was performed for a shorter duration (3months) compared to 6 months duration in the other studies. One study showed that 20mg simvastatin decrease ESR level significantly when used for 6 weeks [22], which may be attributed to different anti-inflammatory properties of statins [23].

Serum CRP level is the best biochemical indicator of disease activity in RA patients [24]. Serum CRP level changes more quickly than ESR.With sufficient stimulus, CRP can be increased within 4 to 6 hours and normalized within a week [25]. In addition, CRP elevation is directly correlated with RA disease activity [24].

Serum CRP level in the current study decreased significantly by atorvastatin (less with placebo) with a significant difference between the two groups only in the first month. This finding may be due to the decrease in the number of patients in the second and third month. But this result was compatible with many studies using 40mg atorvastatin in RA patients [19-21], and the same result was found after using 20mg simvastatin [22]. In the METEOR study, 40mg rusovastatin reduced CRP level significantly when compared to placebo [26]. While using 10mg rusovastatin for 12 months [27] or 80mg atorvastatin for 12 weeks for 11 RA patients [8] showed no significant improvement in CRP.

Assessment of tender points is considered as the cornerstone during evaluation and treatment decision making in RA [28]. In the present study, TJC was significantly decreased by atorvastatin (-66.16%) compared to pretreatment, while placebo showed non-significant decrease in TJC. Moreover, there was a significant difference between the effect of atorvastatin and placebo at the second month of treatment with no difference at the end of the study which may be due to decreased number of patients at the third month. A similar finding was reported in El-Barbary and co-workers (2011), where 40mg

atorvastatin produced a significant decrease in TJC compared to placebo. Two other studies on simvastatin and statins respectively showed a significant decrease in TJC compared to placebo[22,29]. Other trials showed non-significant decrease in TJC when atorvastatin was used compared to placebo. The difference from our findings may be due to the inclusion of mild RA patients [19] or due to low number of patients [8].

Swelling of joints are considered as the best single variable that detects response to drug therapy in RA patients [30]. In the present study, SJC was significantly reduced by atorvastatin compared to placebo. This finding was confirmed by several trials when atorvastatin as adjuvant therapy was used for six months in rheumatoid arthritis patients [19, 21]. In addition, another large cohort study about using statins in RA patients showed decreased number of swollen joint [29]. Another study using 80mg atorvastatin for 3 months showed non-significance improvement in SJC [17], and this finding may be attributed to small number of RA patient in this study (n=11). One other study where 20mg simvastatin was used showed non-significant decrease in SJC [22]. A similar finding was observed when 10mg rusovastatin was used for 12 months [27] and those different findings may be attributed to different anti-inflammatory potency of statins.

Visual analogue scale (VAS) was shown to be a valid measure of pain intensity in RA patients [31]. In the current study, VAS was significantly reduced by both atorvastatin and placebo, though atorvastatin showed a greater percent of reduction, with no significance difference between them. Several studies confirmed this finding when 40mg atorvastatin was used for RA patients for six months [19, 21] and 80mg atorvastatin for 3 months [8]. While in another cohort which used statin showed a significant difference between the effect of statins and placebo, and this different finding could be due to inclusion of different statins rather than specific one which lead to different anti-inflammatory properties [23].

DAS28 remains the most extensively validated activity index for RA patients [32] to observe the clinical response of the patients to the treatment. Results of the present study

showed that both atorvastatin and placebo produced significant improvement in DAS28 scores after 12 weeks of therapy, though atorvastatin produced a greater percent of the reduction, with no clinical significance between the two groups. Similar results were reported for using atorvastatin 40mg in moderately active RA patients, at which atorvastatin and placebo improved DAS28 but the level of significance was higher in atorvastatin arm [20]. Another large cohort study demonstrated that there is no statically significant difference between placebo and statin on RA disease activity [29]. A third double blind study showed a comparable effect of 80mg atorvastatin and placebo on DAS28 when used for 12 weeks [8]. Two other studies [19,21] reported a significant improvement in atorvastatin group compared to the placebo group. The difference in the results in those trials from the current study may be due to many reasons: The dose dependent pleiotropic effect of statins [33] may be responsible for our finding of no more benefit of atorvastatin than placebo because of the use of low dose atorvastatin (20mg) in the current study whereas in other studies a higher dose of atorvastatin 40mg was used. Moreover, the shorter period of follow up and smaller sample size in the current study may be a potential reason for such difference compared to the two other trials.

Conclusions

It can be concluded that 20mg atorvastatin is a safe and well-tolerated drug that has modest anti-inflammatory effect in patients with moderate to highly active RA. It also has the ability to reduce C-RP level, SJC and TJC but with less effect on ESR, VAS and DAS28 when compared to placebo.

Recommendation

Larger scale multicenter clinical trials are required to support the reported data. In addition, evaluation of the effect of higher doses of atorvastatin in patients with moderate to highly active RA should be taken. Longer period of follow up are required to evaluate long-term benefit of atorvastatin on RA disease activity.

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TOFIQ Journal of Medical Sciences, TJMS, Vol. 1, Issue: 1, 2014
Pages: 32-46

History and Concept of Islet Cell Transplantation

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Abstract

Diabetes Mellitus is a chronic disease characterized by a conglomeration of metabolic disturbance of carbohydrate and fat metabolism. Since its recognition around 1500BC, its management was always a challenge for practitioners and has gone through a series of milestones starting with the introduction and use of Insulin in 1921; an established standard for treating Type I diabetes, followed by the introduction of Pancreatic transplantation which was firstly performed in 1966, culminating with the era of Islet cell transplantation which has propagated to a promising pace since 1972. The Edmonton protocol of Islet cell transplantation, which was introduced by Shapiro et al in 2000, adopts an innovative use of immunosuppression drugs with fewer side effects. This paper outlines the historical propagation of treating type 1 diabetes. It highlights the advent of using islet cell transplantation as a newer noninvasive means of providing persistently endogenous insulin for type 1 diabetic patients. This is considered a better accepted way of restoring euglycemia with the merit of avoiding attacks of hypoglycemia which is a well-known side effect of Insulin therapy. Once a dream, islet cell transplantation for treatment of diabetic patients was never as close to being a reality as it is today. We can now see the light at the end of the tunnel through the dramatic discoveries including newer technologies to overcome the prolonged need for immunosuppression, the use of encapsulated islet xenografts, the generation of the unlimited supply of human β cells, and the use of embryonic and adult stem cell.

TOFIQ Journal of Medical Sciences, TJMS, Vol. 1, Issue: 1, 2014
Pages: 32-46

History and Concept of Islet Cell Transplantation

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Introduction

Diabetes Mellitus (DM) is a historical disease that drew the attention of humanity since its recognition around 1500 BC by ancient Egyptians, describing a rare disease in which a person urinates excessively & losses weight. It was not until 1600 years later that the Greek physician Aretaeus, recognized that the urine of the affected persons has a sweet taste, coining it for the first time as Diabetes (Poretsky 2009). According to the World Health Organization (WHO), 347 million people worldwide have diabetes and it is the cause of mortality of 3.4 million every year (Danaei 2011, WHO 2009) . WHO further predicts that deaths from Diabetes would double between 2005 and 2030 (WHO 2013). A formerly labeled rare disease is now announced as a global pandemic posing a challenge to public health agencies worldwide.

Diabetes is a complex heterogeneous disorder characterized by hyperglycaemia caused by a total lack, decrease or diminished effectiveness of circulating insulin. Genetically both Type 1 (T1D) and type 2 diabetes (T2D) are polygenic disorders, and multiple genes and environmental factors contribute to the development of the disease (Ounissi-Benkalha 2008, Stolerman 2009).

T1D occurs predominantly in children and young people and is due to selective auto immune destruction of β cells leading to absolute insulin deficiency (Mathis 2001). On the other hand patients with T2D have a strong family history of T2D, more so than in T1D. Type 2 Diabetes mostly affects older people who consume high calorie diet and with relatively sedentary life style leading to a state of cellular insulin unresponsiveness (Insulin resistance) resulting in increase of pancreatic insulin secretion. The resultant β cell exhaustion necessitates the need of exogenous insulin in the patients' therapeutic regimen (Costa 2002). T1D affects millions of individuals and is associated with multiple medical problems due to the relatively longer life span of the affected persons. Premature atherosclerosis is a cause of substantial morbidity and mortality in T1D and tight control of glycemia was found to reduce the risk of developing cardiovascular disease (Costacou 2007, Nathen 2005). However, intensive insulin treatment is associated with three fold increase in severe hypoglycemia,

an obstacle in attempts to attain good glycemic control (DCCT 1993).

Pancreatic Islet Cells

Identified in 1869 by Paul Langerhans, the islets are the endocrine cells of the pancreas which secrete their hormones directly to the blood (Langerhans 1869). The islets constitute 1-2% of the mass of the pancreas. A healthy adult pancreas contains about one million islets, each islet measuring 0.2 mm in diameter, with a combined mass of the islets of 1 to 1.5 grams (Sleisenger 2009). Islets are distributed among the exocrine tissue of the organ. Each islet is surrounded by thin fibrous connective tissue capsule which is intermingled with the connective tissue of the pancreas. In humans four main cell types are found within the islets; α cells secreting glucagon, β cells secreting Insulin, δ cells secreting somatostatin and γ cells secreting pancreatic polypeptide. Within the islet architecture, human islets display alpha and beta cells in close relationship with each other throughout the cluster (Brissova 2005, Cabrera 2006). The clusters of the islets are embedded in a network of capillaries. The flow of blood in this glomerular-like vasculature is regulated by signals, such as nutrients and hormones from remote tissues. Islets have a portal circulation, with blood flowing from beta to alpha to delta cells (Samols 1988). In addition, islet perfusion determines communication between endocrine and exocrine cells (Ballian 2007).

Implementation of Insulin Therapy in Type 1 Diabetes

Insulin therapy is the gold standard for treating people with T1D. The rationale of intensive treatment of type 1 diabetes was introduced after the establishment of the modern standard of care for the medical management of type 1 Diabetes Mellitus by the Diabetes Control and Complications Trial (DCCT) in 1993 and its follow up study; Epidemiology of Diabetes Interventions and Complications (EDIC) (Nathan 2005, DCCT 1993) . After assigning 1441 patients to either conventional or intensive treatment (by applying multiple daily measurements of blood glucose levels with the combination of daily insulin injections of long, intermediate & short acting insulin in addition to dietary and psychological support) the study showed better glycemic control and less secondary complication rates in the intensive treatment group than in the conventional group, rendering the intensive treatment an accepted norm in Diabetes management. Despite better microvascular outcomes, intensive insulin therapy was hindered by a high rate of frequent and severe hypoglycemia (62 episodes per 100 patient-years of therapy).

Rationale for Insulin Producing β Cells Transplantation

The restoration of β- cell mass and reversing diabetes was the reverie of scientists since the recognition of the role of pancreas in treating diabetes. Logically, this needs to be accomplished by two approaches; either by endogenous regeneration of β cells or by transplantation of β cells from exogenous sources. Advances in both approaches are promising. Regeneration of β cells from embryonic and adult stem cells or pancreatic progenitor cells is work in progress that is beyond the scope of this review (Bonner-Weir 2005).

Transplantation of Insulin producing β cells was performed earlier as a vascular procedure by transplanting the whole pancreas (The world first clinical pancreas transplant was performed at the University of Minnesota in 1966 to treat a uremic diabetic patient) (Kelly 1967) . This approach proved to be a cost effective option that offers independence from exogenous insulin, with favorable glucose levels. The procedure proved to ameliorate the complications of DM and improve the quality of life and patients' life expectancy (Fioretto 1998, Navarro 1997). Since that time more than 15000 pancreas transplants has been performed around the World with 85% one year graft survival rate, and with insulin independent recipient (Sutherland 2001) . The DCCT provided a strong ground for using pancreatic transplantation. It provided evidence that simultaneous kidney and pancreas transplantation is the treatment of choice for most diabetic people with end stage renal failure with a 3- year survival rate of approximately 70- 80 % , simulating the rates for most of other organ transplantation (Gruessner 2001) . Kidney biopsies had shown dramatic reversal of the mesangial accumulation and basement membrane thickening 10 years after the establishment of normal glycemia following pancreas transplantation. Of note is that macrovascular complications as well as the sensory, motor and autonomic neuropathy were stabilized (Fioretto 1998, Fiorina 2001).

Historical Aspects of Islet Transplantation

1. Pancreas Transplantation

The concept of transplanting extracts or pieces from the pancreas to patients with diabetes dates back to 1894 when Williams used minced sheep's pancreas for oral and subcutaneous therapy. This adventurous trial proved a failure, presumably due to using xenografts without immunosuppression (Williams 1894) .

It was not until 1972 that a successful trial by Ballinger and Lacy of transplanting isografts from normal rats to streptozocin induced diabetic rats could reverse diabetes (Ballinger 1970) .

Islets autografts were transplanted successfully in 1980. This was performed on a patient with painful chronic pancreatitis in whom the pancreas was removed, minced, digested with collagenase and unpurified preparation of islets was re-infused into the patient portal vein. Being large in size the islets lodged in the liver without reaching the sinusoids (Sutherland 1980). In the 1990s, some promising reports were documented, with some recipients showing insulin independence for up to one year after the procedure. Wahoff et al. reported insulin independence rate of 74% two years after autologous islet transplantation in 14 patients receiving portal vein infusion of islet cell extracts from their removed pancreas (Wahoff 1995). Trials during the years 1990 to 1995 showed success in only 6 percent of the islet transplants (Hering 1996). The Islet Transplant Registry records of 267 patients who had undergone islet allograft transplantation showed that 12.4% of patients were insulin independent for 7 days. Only 8.2% of them stayed independent for one year (Brendel 1999). It is worth mentioning that these early trials adopted an immunosupression protocol using anti-lymphocyte globulin combined with Cyclosporine, azathioprine and corticosteroids. The use of immunosuppression in transplantation procedures is a considerably challenging issue due to the balance sought between their efficacy and their toxicity to the islet cells. These drugs are diabetogenic as they were found to increase the peripheral insulin resistance. In addition, they have an antiproliferative effect on the engrafted tissue (Ishizuka 1993, Hyder 2005, Lohmann 2000). The high concentration of these drugs in the liver imposes more risk to the engrafted islets at their site of lodgment in the liver sinusoids.

2. Islet Cell Transplantation

Despite the improvement in insulin therapy in treating T1D, many patients are disabled by the refractory hypoglycemia. Compared to pancreas transplantation, introducing cell-based therapy by transplanting islet cells provides minimally invasive means to restoring euglycemia with the avoidance of the complications of surgical procedures. Islet cell transplantation underwent a substantial progress during the last three decades (Hering 1999, Ricordi 2004). Few centers performing the procedure have shown high rates of favorable insulin independence in patients with T1D.

The use of newer immunosuppressive agents was introduced in 2000 at University of Alberta, Edmonton by Shapiro et al who developed a corticosteroid-free

immunosuppressive protocol that includes Sicrolimus, low dose tacrolimus and a monoclonal antibody against interleukin-2 receptor (Daclizumab) for use in trial of islet transplantation in patients with brittle T1D (Shapiro 2000) .

The trial reported 100% success rate of restoring normal glycemia in seven patients during a median follow up of 11.9 months. This was achieved by applying more rigorous criteria to attain sufficient mass of transplanted islets to achieve normal glucose levels. The new approach resulted in sustained freedom from the need for exogenous insulin with better outcome when compared to previous reports (Brendel 1999). However, five years later the results of Edmonton Protocol showed some discouraging trends. Only 15% of the patients were free of exogenous insulin treatment although 85% still showed evidence for the presence of plasma C- peptide which is an indication of endogenous insulin secretion by the transplanted islets (Shapiro 2005).

An international multicenter trial of the Edmonton Protocol was conducted to explore the feasibility of islet transplantation with the use of the Edmonton protocol (Shapiro 2006). Thirty-six subjects with T1D were recruited from 9 centers. The islets were obtained from pancreata of deceased donors and transplanted within two hours after purification. The primary end point was insulin independence one year after the final transplant. Of the 36 recipients, 44% met the primary endpoint (Hemoglobin A1c <6.5; Fasting blood sugar <140 mg/dl; Post prandial sugar <180 mg/dl). Twenty eight percent had partial function of islets (C peptide > 0.3 ng/ml). Twenty eight percent had graft loss one year after the final transplantation and 58% had insulin independence at any point throughout the study. The multicenter study confirmed the former experience with the single center Edmonton protocol and demonstrated the benefit of islet transplantation in patients with brittle T1D. It proved that even in patients with residual islet function, severe hypoglycemic episodes were minimized. The trial also standardized pancreas selection, recipient selection, islet processing and post transplantation care.

Indications of Islet Transplantation:

1. Autologous Islet Transplantation in pancreatectomy- induced diabetes, if the pancreas is affected by trauma, chronic pancreatitis or benign neoplasms.

2. Allogenic Islet Transplantation is indicated in T1D as Islet transplantation alone (ITA), Simultaneous islet and kidney transplantation (SIK) and as Islet after kidney transplantation (IAK) (Pileggi 2004).

3. Allogenic transplantation is indicated in patients with diabetes having other metabolic disorders like cyctic fibrosis and hemochromatosis (Lanng 1992) .

4. Other rare indication is in people with T2D and liver cirrhosis, although advanced patient's age and comorbidity are contraindications to this procedure (Ricordi 1997).

Islet Transplantation Technology:

The modern islets isolation technology includes:

1. Procurement of healthy pancreas from brain dead donor whose heart is beating. Recently cadaveric donors are being used successfully.

2. Cannulation of the pancreatic duct, collagenase infusion to dissociate islets from exocrine, ductal and surrounding connective tissues.

3. Distended pancreas is cut into smaller pieces and transferred into so-called Ricordi's chamber, where digestion takes place to liberate and remove the islets from solution. (A recipient needs more than 12,000 islet equivalents/ kg; IE, the number of islets normalized to an islet of 150 µm of diameter). Around 5000 IE/kg can be obtained from one pancreas. Islet isolation may cost around $10,000 US)

4. Purification of the islets from the enzyme by centrifugation, to minimize the volume of the tissue to be implanted by separating the exocrine tissue and debris, hence decreasing the insult to the liver to prevent portal hypertension.

5. Transplantation; either immediately or after culturing for a short time to assure sterility and to assess in vitro the function of islet preparation. In addition, culturing helps in modulating the islets regarding immunogenicity and induction of cyto-protective molecules, and genetic modification of the islets before transplantation.

These strategies were required to reduce the coagulation/ complement activation and inflammation which may cause islet tissue rejection by the recipient (Villiger 2005). Culturing also helps in preconditioning the recipient regarding immune suppression and reduction of inflammation (Pileggi 2006).

6. Islet infusion to the recipient under conscious sedation, using ultrasonic or fluoroscopic guidance. Islet cells infused though a needle introduced via the skin into the right portal vein. The implants are then engrafted into the liver sinusoids and are ready to function. The islet infusion can be repeated on several occasions to deliver the appropriate amount of islets to achieve the optimal glycemia (Robertson 2004).

7. Other sites for infusion are the kidney capsule, spleen, testes, peritoneal cavity, small bowel, intramuscularly, and subcutaneously.

8. The situation after the infusion may not be favorable and many islets fail to engraft and function. This can be attributed to the prolonged hypoxia during the revascularization period which may take about two weeks. In addition the risk of bleeding when anticoagulation or antiplatelet drugs are used during the infusion as well as the blood mediated inflammatory reaction secreting inflammatory cytokines by the recipient lymphocytes which contribute to apoptosis and necrosis of the newly harbored β cells. The process of rejection peaks in two to three days and ends by two weeks (Hyder 2005). Another challenge that might affect the function and viability of the engrafted islets is the antiproliferative effect of immunosuppressive drugs which hinders angiogenesis for the newly transplanted islets.

Clinical Effect of Islet Cell Transplantation

Few papers discuss the clinical effects of islet transplantation on type 1 diabetic patients regarding morbidity and mortality. One paper studied the effect of islet transplantation on patients' survival. Comparing two groups who had kidney islet transplant; one group showed C peptide secretion > 0.5ng/ ml and the other lost C peptide with early failure of the engrafted tissue. After seven years of follow up, the successful group with sustained restoration of β cell function had significantly higher survival rate (90%) than the other unsuccessful group (51%).

The higher survival in the successful group was accompanied by higher C- peptide levels and lower insulin requirement compared to the unsuccessful group, despite similar glycated hemoglobin levels. The cardiovascular deaths were higher in the latter group with poorer atherosclerotic profile and endothelial function (Fiorina 2005)

Effect of Islet Transplantation on Long Term Diabetes Complications

No controlled studies have addressed the question whether Islet transplantation can halt or delay chronic diabetic complications. This is attributed to the difficulty of performing large clinical trials in the lack of standardized protocols, the variable methods of isolation of the islet tissue and the use of different immunosuppressive measures.

Animal studies had shown that Islet transplantation can improve cases of diabetic cardiomyopathy. An uncontrolled study on a small number of patients showed improvement in cardiovascular function over 3 years follow up period in kidney transplant recipient with functioning islet transplants (Laviola 2001) .

One of the results of this study was the delay in intima medial thickening and improvement in atrial and ventricular function

Nephropathy is one of the most common chronic complications of T1D (DCCT 1993). DCCT demonstrated a reduced incidence of microalbuminuria in type 1 diabetic patients in the intensive group compared to the conventional group. A paper published in 2003 showed that successful islet transplantation in T1 diabetic patients with end stage kidney disease receiving kidney transplant had prolonged graft survival and prevent reduction in vascular function of the graft (Fioina 2003). Better renal vascular function was demonstrated in another group of patients with kidney transplant and functioning islet transplant compared to the group without functioning islets (Fiorina 2005).

Diabetic retinopathy is a well-recognized complication of diabetes (DCCT 1993). It is characterized by new vessel formation and reduced retinal blood flow, hypoxia and distorted endothelial integrity (Miller 1997). A recent case control study on 10 patients who received islet transplantation alone compared with a control group of type 1 diabetic patients used a color-Doppler-imaging to study the effect of ITA after one year on the blood flow velocities of central retinal artery and vein.

A statistically significant increase of blood flow velocities of central retinal arteries and veins was found only in the ITA patients (Frank 2006). An early, significant increase of arterial and venous retinal blood flow velocities was found after ITA .

Peripheral nerve function was assessed with a nerve conduction velocity (NCV) index in islet transplanted patients in a 2 years follow up study. There appeared to be a positive effect of β cell implantation on polyneuropathy. This study did not provide a statistical analysis (Lee 2005). Another report indicated that islet transplantation can induce long lasting stabilization or even improvement of poly neuropathy in type 1 kidney transplanted diabetic patients who received functioning islet transplant (Del Carro 2007).

Conclusion

Islet transplantation is an evolving therapeutic measure for highly selective patients with severe hypoglycemia or labile T1D. It remains at cross roads due to the critical shortage of donor organs, the poor long term results, and the relatively high incidence of adverse effects as well as its high cost. Therefore the procedure is still unsuitable to be expanded to the general population.

Nonetheless the dramatic discoveries and the expansion of the horizon to include newer technologies which overcome the issue of prolonged need for

immunosuppression by using encapsulated islet xenografts, generating an unlimited supply of human β cells, and the use of embryonic and adult stem cell, set the stage for a dream come true in transplanting islets cells to treat diabetic patients.

Conflict of Interest: The author reports no conflict of interest.

The work is original and had not been published or submitted elsewhere.

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MESH REPAIR VERSUS PLANNED VENTRAL HERNIA STAGED REPAIR IN THE MANAGEMENT OF TRAUMA PATIENTS WITH ACUTE ABDOMINAL COMPARTMENT SYNDROME

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Summary

Background: The terms Intra-abdominal hypertension (IAH) and Abdominal compartment syndrome (ACS) are commonly used interchangeably; however it is important to recognize the distinction between these two terminologies. Recently, at the World Society on Abdominal Compartment Syndrome (WSACS), the threshold for IAH and ACS was established as a value ≥ 12 mmHg and > 20 mmHg respectively. Patients with either ACS (defined as a sustained intra-abdominal pressure- IAP) or IAH can be effectively managed via decompression followed by mesh repair (MR) or staged repair (SR) method

Objectives: This research aims to evaluate the results of mesh repair in comparison to planned ventral hernia staged repair for closure of abdominal wall defects after decompression in trauma patients with (ACS).

Patients and methods: All patients with major abdominal trauma and identifiable risk factors for development of ACS presented to the first surgical unit in Baghdad Teaching Hospital between the 1ST OF March, 2005 and the 30th of September, 2008 were enrolled. IAP was measured indirectly using intravesical pressure in most cases.

Patients were screened for IAH/ACS risk factors during the operation and/or upon admission into the surgical ward or ICU. If one risk factor was present, baseline IAP measurement was done but If two or more risk factors were present, an additional serial IAP measurements was performed every 4-6 hr in the first 24 hours. Those with grade IV or ACS on initial measurement or during follow up urgently underwent decompression. Bogota bag was used in the initial phase of closure of abdominal wall defects. Patients were randomized into either the Mesh Repair Group (MRG) or the planned ventral hernia Staged Repair Group (SRG).

Results: A total of 663 patients were enrolled in this study. The mortality rate in the group with normal IAP was 3.5%, contrary to a much higher mortality rate of 19.6% in those with elevated IAP. The mortality rate in the SRG was higher than the MRG. Overall complications incidence was much higher in the SRG (85.7%), in comparison to the MRG (56.3%). The incidence of wound infection, intra abdominal collections, dehiscence and ileus with intestinal obstruction were compared in both groups. The occurrence of intestinal fistulae was higher in the SRG (28.8%) than in the MRG (6.3%) ($P<0.04$). The mean hospital stay was 15.2 days/patient in the MRG but 26.1 days/patient in the SRG (after adding those of the repair of ventral hernias).

Conclusion: ACS is a serious complication in surgical wards but it is often overlooked as a case of subsequent serious complications unless it is suspected early and managed properly. The use of mesh repair to close abdominal defects after decompression for ACS reduces mortality and morbidity in comparison to the use of planned ventral hernia staged repair.

Key words: Intra-abdominal hypertension, abdominal compartment syndrome, mesh repair, staged repair

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INTRODUCTION

The concept that the abdominal cavity can be considered as a compartment had been known since the end of the nineteenth century [(1)] but has only recently become the subject of interest and discussions [(2)].

The terms Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are commonly used interchangeably; however it is important to recognize the distinction between these terminologies. IAH exists when IAP exceeds a measured numeric parameter. This parameter has generally been set between 20 to 25 mmHg [(3,4)]. Recently at the (WSACS), the threshold for IAH was established as a value of 12 mmHg or greater while ACS, defined as a sustained IAP was established as a value > 20 mmHg with or without an abdominal perfusion pressure (APP< 60 mmHg) that is associated with new organ dysfunction or failure. However, most surgeons advocate urgent decompression if IAP exceeds 25 mmHg, in the absence of new organ dysfunction [(5)].

Clinical confirmation of IAH requires either indirect bedside tests that measure IAP from transduction of intravesical, gastric, rectal, vaginal, and caval pressures, or direct measurement by an intraperitoneal catheter [(6,7,8)].

The clinical triad of oliguria, hypoxia, and elevated central venous pressure in association with abdominal distension indicates a late diagnosis with impairment of one or more systems. Decompressive laparotomy, in such occasions should be done as soon as possible to prevent Multiple Organ Failure Syndrome (MOFS), without attempting at measuring IAP [(9)].

Treatment of abdominal wall after decompression is controversial. Some advocate primary repair with mesh, however most surgeons advocate two stage repairs for abdominal wall reconstruction. Firstly, temporary closure of the abdomen is performed; which can be done by different methods such as Bogota bag, the Vacuum Assisted Closure (VAC) technique, Wittmann patch (velcro burr), silo, or absorbable mesh [9,10, 11, and 12]. This study was performed to evaluate the results of mesh repair in comparison to planned ventral hernia staged repair for closure of abdominal wall after decompression in trauma patients with (ACS).

PATIENTS AND METHODS

All patients with major abdominal trauma and identifiable risk factors for development of ACS presented to the First Surgical Unit in Baghdad Teaching Hospital, Iraq were enrolled for this research. The following risk factors were addressed; prolonged pre- and/or intraoperative hypotension (SBP<90mmHg), polytransfusion >10 units blood in 24 hr, massive fluid resuscitation >5L crystalloid and/or colloid in 24hr, retroperitoneal, intraperitoneal, and preperitoneal hemorrhage, abdominal distension (gastric dilatation, ileus, and intestinal obstruction), tight abdominal closure, massive trauma, massive burns, damage control surgery (hypothermia, acidosis, and coagulopathy), prolonged surgery >4 hr, and medical co-morbidity (obesity, ascites, ARDS, and respiratory failure).

IAP was usually measured indirectly using intravesical pressure in most cases while in few patients the measurement was done using nasogastric tube in the stomach to measure the intra-abdominal pressure . First Foley catheter with an appropriate size was positioned in e place, if not already present. The urinary bladder was evacuated, and a 25-50 ml of sterile saline (1 ml/kg for children below 25kg in weight) was injected into the bladder via the aspiration port of the catheter. The sterile tubing of the urinary drainage bag was cross-clamped distal to the drainage port. A hand-held manometer was connected to the Foley catheter, and the pressure in cm H_2O was recorded via the height of the water column in the manometer. This was expressed in mmHg by dividing it by a factor of 1.36 .

The test was performed in supine position, at the end of expiration, and the pressure was zeroed at the iliac crest in the midaxillary line. The pressure was measured every 30-60 seconds after instillation of saline to allow relaxation of the bladder detrusor muscle. There should be no muscle contraction, as this could lead to a falsely high result. Intragastric pressure was occasionally used in patients with genitourinary pathology or trauma.

Patients were screened for IAH/ACS risk factors during the operation and/or upon admission into the surgical ward or ICU. If one risk factor was present, baseline IAP measurement was done but If two or more risk factors were present, an additional serial IAP measurements were performed every 4-6 hr in the first 24 hours. If baseline IAP (i.e. <12 mmHg) or serial IAP records were normal on follow up, a close follow up for development of organ failure was done for another 24 hr. However, on a steady increase of IAP, a serial measurements of IAP were done every 2hr. Urgent decompression was performed if two readings confirmed elevated IAP > 25 mmHg. According to the (WSACS) definition of IAH and ACS, IAH can be graded into four grades; normal (less than 12mmHg), grade I (IAP 12-15 mmHg), grade II (IAP 16-20 mmHg), grade III (IAP 21-25 mmHg) and grade IV (equivalent to ACS).

For patients in grade I, serial measurement of IAP was done every 4-6 hr, but every 2 hrs for grade II. Maintenance of normovolaemia in these two groups was imperative. For grade III patients, additional medical measures were done such as gastrointestinal decompression with NG tube, prokinetics like metaclopromide, analgesics, sedatives, and use of colloids rather than crystalloids to reduce interstitial oedema.

Those with grade IV or ACS on initial measurement or during follow up urgently underwent decompression. Abdominal decompression was also performed primarily as a prophylaxis, when very tight abdominal closure was anticipated, and as a general rule, when the intestines lie above the level of the skin in a fully relaxed patient under neuromuscular blockade of general anesthesia, IAP would be higher than 25 mmHg, if closed primarily.

Once decompression was completed, rapid but thorough examination of the abdominal cavity was performed to identify and control, if possible, any cause of IAH. The initial phase of closure of abdominal wall defects implies the use of temporary closure method. There are multiple methods for temporary closure, but Bogota bag was used in this study. It is either an IV fluid bag or more commonly 2L urinary bags that are cut-open, and sutured to the skin or fascia with a continuous heavy nylon suture. The bag is then covered with Betadine-soaked Laparotomy packs, which are changed daily in the surgical ward or intensive care unit. Occasionally, the bag is changed, if signs of infection are present.

Cardiovascular stability and resolution of sepsis were indication to transfer patient to the theatre for removal of the bag and closure of abdominal wall defect. This phase is normally done five days to three weeks after decompression. Those who require a long period to recover, have their Bogota bag changed on a weekly basis, to reduce the risk of infection.

Patients booked for definitive closures of their abdominal wall defects were randomized into either the Mesh Repair Group (MRG), or the planned ventral hernia Staged Repair Group (SRG). Those who underwent staged repair, had their abdominal wall defects closed with skin undermining to the flanks and closing it in the midline for small defects (< 6cm wide), or secondary meshed split-thickness skin grafting, when healthy granulating tissue had covered the thin peritoneum over the bowels for larger defects (> 6cm wide). The latter was achieved in conjunction with a plastic surgeon. The second stage was performed 3-12 months later; this consists of the repair of any resultant ventral hernia.

Statistical analysis

Statistical analysis was performed using GraphPad InStat 3. Variables were compared using Fisher exact test with two sided P-value.

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Means of continuous variables were compared using Student's t-test. Factors contributing to the development of suture line failure were determined using logistic regression analysis. Statistical significance was defined at $P < 0.05$.

RESULTS AND DISCUSSION

A total of 536 male patients (80.8%), and 127 female patients (19.2%), were enrolled in this study. Ages of patients ranged between 10-72 years, with a mean age of 28 years (26 years for males, and 36 years for females). 52% of the patients were within the age range of 10-30 years. Eighty six patients (13%) had blunt trauma to abdomen, while 577 patients (87%) had penetrating trauma. The mean injury severity score (ISS) was 24.

IAP was normal in 566 patients (85.4%). Elevated IAP was noticed in 97 patients (14.6%) while 44 patients (6.6%) had grade IV IAH, and ultimately needed decompression. Twenty three patients (3.5%),14 patients (2.1%) and 16 patients (2.4%) had grade I IAH, grade II IAH and grade III IAH, respectively and were treated with conservative measures.

Out of those who underwent decompression, six patients died before definitive closure of their abdomen. Sixteen patients (43.2%) underwent mesh repair (The MRG). The mesh was covered with secondary skin grafting in six (38%) patients, while primary skin closure over the mesh was done in the other 10 patients (62%).

In contrast, 21 patients (56.8%) underwent staged repair SRG. Skin closure was done primarily in 16 patients (76%), while secondary skin grafting was done for the remaining 5 patients (24%). However, only 13 patients of the SRG had their ventral hernias ultimately repaired, 8 patients could not repair theirs due to either unfitness or/and unwillingness of the patients for multiple procedures. Although there was no mortality among those who underwent ventral hernia repair (VHR), complications of this operation were added to the SRG, as VHR comprises part of the staged repair of the ACS.

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The MRG include 14 male patients (87.5%), and two female patients (12.5%), while the SRG had 17 male patients (81%), and 4 female patients (19%). There was no ender and the surgical procedure (P-value = 0.47).

The mean age of the MRG was 27 years (12-61 years), while the mean age of the SRG was 30 years (10-65 years). There was no statistically significant difference between the two groups (P-value=0.21).

There were no statistically significant differences between the two groups with regards to the mechanism of injury (P-value = 0.52), mean injury severity score, ISS (P-value= 0.61), and the need and duration of ICU admission before the application of definitive treatment (P-value= 0.48, and 0.84 respectively).

The mean duration between decompression and definite treatment was 8.4 days in the MRG, and 9.2 days in the SRG with no statistically significant difference between the two groups in the duration of the initial phase of treatment (P-value= 0.90).

The mortality rate was 3.5% in the group with normal IAP in contrast to a mortality rate of 19.6% in those with elevated IAP (P-value < 0.0001). Those who needed decompression accounted for its major part, as the mortality rate in this group approached 36.4%. Six patients (13.6%) died in the initial phase of the treatment after decompression. Three patients (6.8%) died in the MRG while 7 patients (15.9%) died in the SRG. There was no statistically significant difference between the MRG and SRG as regards to mortality with a P-value= 0.46) .

The overall complications incidence was much higher in the SRG (95.2%) in comparison to the MRG (56.3%), with a P-value < 0.01 but in general there were no statistically significant differences between the two groups regarding wound infection, intra-abdominal collections (pelvic or subphrenic), dehiscence, and ileus with intestinal obstruction (Table 1).

Intestinal fistula is a serious and dreadful complication of exposed abdomen for prolonged periods. It is unavoidable and very difficult to heal. A patient (6.3%) developed intestinal fistula in the MRG while six patients (28.8%) developed intestinal fistulas in the SRG.

Intestinal fistulae were less in the MRG than in the SRG P-value< 0.04). One patient in the MRG and four patients in the SRG died as a result of this complication.

T. Jernigam (???), in his research on 167 patients showed that 14 patients (8.4%) developed fistula amidst various kinds of management; ten out of the 14 were in the MRG. In addition Torrie [21] reported 6(9%) fistula in his study on 68 patients using only mesh repair method.

These differences in results are possibly related to the mechanism of trauma, presence of bowel injury and duration of mesh application prior to coverage of granulating wound which appears to be a major contributor to these results.

Dehiscence, another serious and difficult-to-treat complication associated with exposed abdomen occurred in two patients (12.5%) in the MRG, and was treated by removal of the mesh, refreshing the edges, and reapplication of the Bogota bag, which was changed accordingly, until infection resolved and healthy granulation tissue was gained, when definitive treatment could be reapplied. In contrast, six patients (28.6%) developed dehiscence in SRG; those that occurred as a result of infection (three patients) were treated as previously stated, while those not related to infection, were treated by reclosing the skin (which was done in two patients) and by rectus femoris myocutaneous rotational flap, (done in one patient). There were no statistically significant difference between the two groups (P-value = 0.22). Compared to Torrie (????) who reported dehiscence in 3 cases, many patients in this study had known risk factors for dehiscence; these include raised IAP, wound infection and multiple trauma or malnutrition.

It was generally accepted that wound infection and intra-abdominal collections were mostly related to the more severe injuries, defective management in the wards, incompetent staff and lack of supplies and monitoring devices.

Mean stay-in-hospital was 15.2 days/patient in the MRG and 29.1 days/patient in the SRG (after adding the total days for the repair of ventral hernias) which was statistically significant with P-value <0.05.

Table 1. Comparison of outcome and overall complications between Mesh Repair Group (MRG) and Staged Repair Group (SRG).

Complication	**MRG No. (%)**	**SRG No. (%)**	**P-value**
Total number of cases	16 (43.2%)	21 (56.8%)	…….
Wound infection	2 (12.5%)	4(19%)	0.68
Intraabdominal Collection	2 (12.5%)	2 (9.5%)	0.59
Dehiscence	2(12.5%)	6 (28.6%)	0.22
Fistula	1 (6.3%)	6(28.6%)	<0.05
Ileus/Intestinal obstruction	2(12.5%)	2(9.5%)	0.38
Total complications	9 (56.3%)	20 (95.2%)	<0.01
Mean in-hospital stay day\patient	15.2	29.1	<0.05
Mortality	3 (18.8%)	7 (33.3%)	0.24

The incidence of ACS in all patients admitted to the surgical units during the period of this study was 6.6% as compared to 15% reported by Parsak [(13)] who carried a study on 119 patients which include 68 males and 51 females with a mean age of 55 years. There were 44 deaths for all grades; those who needed decompression which accounted for the major part approached 36.4%. Six patients died at the initial phase of the treatment after decompression, three (18.8%) from the MRG and 7 (33.3%) in the SRG, in comparison to Parsak (15) results, where 40 patients died in total, thirteen (32.5%) from those who needed decompression.

The occurrence of IAH and ACS is on the increase currently, mostly due to improved methods of diagnosis and recognition of the condition. More patients are now being investigated for IAH due to suspicion, as a high index of suspicion is imperative for optimal outcome. If not recognized and treated in time, ACS can result in multi-organ system failure and death. Studies have shown that IAP higher than 20mmHg results in ACS[(5)]. The adverse effects are reversible with the relief of pressure, if done at the proper time.

Traditionally, IAP can be measured indirectly through the urinary bladder using a Foley catheter. This technique was adopted to avoid direct invasive techniques, and was subsequently popularized by Kron et al in 1984[14]. In this study, the intravesical technique was used because it is more applicable and easier to perform than other methods. Further studies are needed to compare their accuracy.

ACS is associated with potentially high mortality that must be recognized early and managed effectively to optimize the outcome. Most deaths associated with ACS are due to sepsis or multiple organ failure. There is a direct correlation between abdominal hypertension and mortality rates[15,16,17]. However, IAP is not the only factor determining survival[18,19]. The presence of co-morbidity is a factor that increases mortality, which was also true for our patient population. Although other factors were not included in this study, the primary etiology, mainly trauma, together with general clinical condition of the patient greatly determine the outcome and prognosis.

Complications encountered during the study include wound infection, intra-abdominal collection, intestinal fistula, dehiscence and intestinal obstruction.

Overall complication incidence in the SRG and MRG was 95.2 and 56.3%, respectively compared to 73.5% in all modality of management used by Parsak (15).

In this study, two patients both in the MRG (12.5%) and in the SRG (9.5%) developed ileus or intestinal obstruction, mostly related to adhesions. The results were comparable to those obtained by Aydin[20], who also clarified no difference in adhesion formation between the two groups.

An open abdominal wound is a great challenge to a surgeon in postoperative management, due to massive fluid loss, heat dissemination and risk of infections. Frequent assessment, care of the wound and replacement of the lost fluids and electrolytes are mandatory. Strict aseptic technique is required for wound care[22].

Mean in-hospital stay in this study was 22 days, 15.2 in MRG and 29.1 in SRG. This is similar to the findings of Torrie (????) and Timothy (????) with a mean in-hospital stay of 20 and 22 days, respectively.

Currently, there are no prospective studies available to show which is the best method or material. Superiority of one material over the other has not been established. The materials advocated are mesh (absorbable, non-absorbable), zipper, adhesive sheets, plastic bag (Bogota bag) and velcro analog[22]. Recent studies have showed that the use of vicryl mesh is preferable, to get rid of several complications encountered with other types.

Polypropylene mesh was used in this study because other types like vicryl, PTFE and polyglactin were not available and our results with this type are comparable to other workers.

However, it is still impossible to specify fixed uniform criteria for preventive use of temporary closure of abdominal cavity, because it will always depend on subjective assessment of the operator regarding the tension of abdominal cavity after approximation of the fascia edges and estimation of the amount by which the content of abdominal cavity may increase or has already increased during tamponade. Nevertheless, the questions still remains, whether it is not more advantageous in hazard patient to carry out the primary closure of abdominal cavity with post-operation IAP monitoring and early ACS diagnostics instead of preventive temporary laparostomy[24].

Conclusions

ACS is not only a serious condition, but also a common scenario in surgical wards and ICU, which is often misdiagnosed as a case of respiratory failure or circulatory collapse. Most residents and some senior doctors are unaware of its lethal complications and how to diagnose it.

The results of this findings showed that the use of mesh repair to close abdominal wall defects after decompression for ACS is associated with reduced mortality and overall complications, in comparison to the use of planned ventral hernia staged repair.

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"MULTIPLE SCLEROSIS IN IRAQ: HISTORY, EPIDEMIOLOGY AND THE FUTURE"

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Introduction:

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) (1). It is the most common cause of disability in young adults after trauma (2). MS is known to show variable prevalence rates, demographic, and clinical manifestations depending on geography and ethnic background. It is generally believed that MS prevalence is low or moderate in Middle Eastern countries (3). The wide variety of clinical manifestations depends on the extent and the anatomical sites of the demyelinating plaques. The functional prognosis of the disease is poor in the late phases of the disease (4).

Common clinical patterns of MS:

1. Relapsing–remitting (RRMS): the most common form (85% of patients). It is characterized by periods of relapses and remissions of neurological symptoms with or without residual disability.
2. Secondary progressive (SPMS): may develop in up to two thirds of patients with relapsing–remitting disease. Patients continue to worsen with or without periods of remission.
3. Primary progressive (PPMS): affects around 10% of patients. Symptoms worsen gradually from disease onset. There are no relapses or remissions although occasional plateaus may occur (1).

Baghdad MS Clinic:

Following the increasing recognition of patients with MS in the nineties seen at different hospitals in Baghdad and the other cities in Iraq and because of the advances in the diagnostic tests for neurological diseases and especially because of the emerging therapies for MS, which used to be perceived as untreatable disease, the idea of establishing a specialized MS clinic started to emerge.

Baghdad MS clinic was one of the first specialized MS Clinics in the Middle East; it was established in 2000 at Baghdad University Hospital (Medical City Teaching Hospital). The clinic was geographically accessible for most of the population in Baghdad and the rest of Iraqi cities. It is a multidisciplinary specialized neurological service with access to neuroimaging, neurophysiological studies and rehabilitation services. The service was virtually free and equally accessible for the entire Iraqi population. One of the main advantages of such service was the collection of data from MS patients which is of great help in setting directions, plans, and research studies. (3) Data from this Clinic was presented at different regional and international conferences.

Clinical and demographic characteristics of MS in Iraqi patients:

The first account for MS patients among the Iraqi population dates back to the 1950s (5). A study by Hamdi in 1975 found that MS was more prevalent in Kurdish people who live in Northern Iraq (6). In an early publication from Baghdad MS Clinic, the clinical and demographic features of Iraqi MS patients were found to be comparable to the so-called "Western type" of MS as seen in Caucasians. These included: age at onset, clinical course, male predominance and older age of onset in PPMS, frequency of initial presenting symptoms, cumulative neurological signs, disability status, and MRI findings. There was a difference in gender ratio and family history. Female to male ratio of 1.2:1 in one study is somewhat lower than the 2:1 or higher ratio in most Western series, but consistent with reports from neighboring countries like Kuwait, Saudi Arabia, and Jordan (3). A large Iranian study reported increasing disease incidence in females between 2002 and 2008 from 2:1 to more than 3:1 (7).

Family history of MS was reported in up to 5.7% of patients (15% or higher figures reported in Western series). Limitation factors to family history reporting include: lack of careful interviews with 1^{st}, 2^{nd} and 3^{rd} degree relatives of the index case, large family size, and communication difficulties (3). Familial aggregation is a well-known phenomenon in high prevalence areas and it is considered rare in Asia (2).

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A comparison study between familial and sporadic MS in Iraqi patients in 2011 found no significant difference in terms of the demographic patterns, clinical course, and presentation.
Higher percentage of RRMS patients with sporadic MS (41.6%) progressed to SPMS compared with familial cases (around 36.4%). This should be taken with

caution as the numbers were small. There was a statistically significant inverse relation between mean age at onset and lag time to diagnosis ie the younger age, the longer lag time to diagnosis (p=0.007). Also, there was direct correlation between lag time to diagnosis and time to second attack (p=0.05). The individual groups did not vary significantly in this regard (2).

A study looking at the disability and prognosis of 500 RRMS cases from the MS clinic in Baghdad showed that older age at onset, pyramidal and sphincter involvement at the beginning of the illness, and relapse rate in the first two years of the disease were poor prognostic factors. On the other hand, Western studies showed that younger age at onset is a poor prognostic factor, likely due to accumulation of disability with time. Gender was found not to affect outcome in that study, which is in contrast to the widely agreed consensus that female patients have better prognosis than male (4). In 2010, a Lebanese group looked at the prognostic factors of MS in Lebanon found no difference from similar predictors in western countries (8).

MS Epidemiology and North South gradient:

There were no well-conducted MS epidemiological studies from Iraq prior to the establishment of the MS Clinic in Baghdad. An increase in reported cases is noticed possibly due to increasing recognition of the disease, better facilities for the diagnosis, and increasing number of neurologists and other specialties dealing with MS. There is an interesting phenomenon of progressive increase in the number of MS patients over the years in the last three decades according to the age of onset, and the low proportion of patients with long duration of the disease. An increase in incidence in the last three decades is a possibility, but this should be accepted with caution. The significant increase of the number of women with MS compared to men in the last three decades might stimulate the pattern of increasing trend in women in the West. The gender shift is difficult to be explained by a changing social structure that might give women more access to medical services. Changing environmental factors might provide one explanation for increasing incidence; a shift towards a more Western lifestyle has been linked to the increase of MS incidence in Japan. In Iraq, economic and social changes have been apparent, especially since the early 1970s and might be a factor (3).

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Looking at data from neighboring countries, a study from Iran estimated MS prevalence in Tehran to be at least 51.9:100,000 (7). However, a more recent study from Southeastern Iran reported a prevalence of around 14:100,000 which is comparable to countries in the region (9).

MS has been shown to increase in prevalence with increasing distance from the equator. In Iraq, MS patients born in Naynawa were more than six times those born in Basra in one study; both governorates have approximately equal population and are roughly equidistance from Baghdad. There is a latitude difference between the two regions; with Naynawa lying on the 29^{th} and Basra on 35^{th} degree. Also, dietary habits are different between the two areas; people in the North eat animal fat rich diet while South residents eat more seafood. Sun exposure and temperatures are more in the South. Thought the majority of people in both regions are Arabs, it's been observed that Iraqis from Naynawa have fairer skin, lighter eye colour, non-Arab and non-Muslim minorities than those from Basra. These differences raise the possibility of different genetic constitutions between Iraqi patients which in turn may affect the susceptibility to develop MS (3). A study from Israel on Arabic MS patients reported more rapid disease course in Druze and Muslims compared to Christians. High relapse rate, annual disability progression, and MS severity scores were higher among the Druze. These findings support the hypothesis of population specific MS phenotypes (10).

The Future:

MS remains a disabling disease with significant impact on people lives. Advances in research in the last three decades provided new treatments for the relapsing forms of MS. More studies are in progress to find solutions for progressive MS patients.

Health services in Iraq have been suffering as a result of wars, sanctions, and slow recovery after 2003. Many skilled health professionals have migrated to other countries, and new graduates continue to leave. A decade has passed since 2003 but the health infrastructure is not fully restored. The healthcare system is centralised and focused on big hospitals (11). The absence of clear strategies in setting up medical services and financial planning are the main reasons why patients with complex diseases are not receiving ideal medical care. There is a strong need for long term planning for conditions like MS where enthusiastic medical profession and reliable management groups work hand in hand to build the basis for medical institutions where healthcare is provided to patients at excellent level.

Conflict of Interest: none.

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THE EFFECTS OF VAGAL NERVE STIMULATION THERAPY IN REFRACTORY EPILEPSY ON THE ELECTRICAL ACTIVITY OF THE HEART

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Key wards: Vagal nerve stimulation, refractory epilepsy, QT, QTp, TpTe intervals and dispersion.

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ABSTRACT:

Background: Refractory epilepsy is a major problem for neurologists and epileptic patients. Vagal nerve stimulation is one of the palliative surgical therapies. Traditionally, the vagus nerve has been considered a parasympathetic efferent nerve (controlling and regulating autonomic functions, such as heart rate and gastric tone). Changes in autonomic nervous system activity affect both depolarization and repolarization phases in addition to heart rate, and thus affect QT interval.

Objective: to evaluate the possible side effect of vagal nerve stimulation therapy on the electrical activity of the heart represented by QT, QTp, TpTe intervals and QT&QTp dispersions.

Patients and method: This study was conducted at Neurosciences hospital in Baghdad, between September 2008 and march 2010.ECG traces were recorded for 32 pharmacoresistance epileptic patients with a mean age 21.14 + 4.4 year, just before and after implantation of the Vagal nerve stimulation device. All QT,QTp and TpTe intervals and QT & QTp dispersion were calculated manually.

Results: there were differences in both QT and QTp before VNS implantation as compared to that after the implant but it did not reach a significant level. Similarly no significant differences were observed in QT and QTp dispersions. An interesting significant difference in TpTe (before and after the implant) was observed.

Conclusion: Vagal nerve stimulation therapy may alter the cardiac conductivity in some cases.

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THE EFFECTS OF VAGAL NERVE STIMULATION THERAPY IN REFRACTORY EPILEPSY ON THE ELECTRICAL ACTIVITY OF THE HEART

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NTRODUCTION:

Approximately one-third of patients with epilepsy continue to have seizures on medication (1). Their seizures are referred to as refractory or drug-resistant. In those with refractory epilepsy, a combination of antiseizure medications may be tried. The combination may help to reduce the total number of seizures. However, polypharmacy often leads to an increased number of side effects. When medications are not enough to control seizures, physicians often turn to nonpharmacologic options: epilepsy surgery, ketogenic diet, and vagus nerve stimulator (VNS) therapy.

The VNS Therapy System was approved as adjunctive therapy for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs. The vagus nerve stimulator (VNS) is a battery-powered device similar to a cardiac pacemaker. Stimulating leads are surgically placed around the left vagus nerve in the carotid sheath and are connected to an infraclavicular subcutaneous programmable pacemaker.

For better understanding of the clinical use & side effect of the VNS; a brief introduction of relevant anatomy, possible mechanisms of action is required,

ANATOMY:

The idea of using the vagus nerve in particular stem out of its unique anatomy. It is widely distributed to both sides of the brain and brain stem structures. The majority of vagus nerve fibers 80% are afferent (sending signal towards the brain) rather than efferent 20% (sending signal away from the brain) (2).

If an electrical stimulus is placed on the vagus nerve, 80 percent of the applied stimulation travels back to the brainstem where the vagus nerve originates. The central projections of the vagus nerve (cranial nerve 10) synapse bilaterally on the nucleus

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of the solitary tract (NTS) in the brainstem. From the NTS, vagal afferent pathways project to many regions in the brain, including pontine and midbrain nuclei, the cerebellum, thalamus, and cortex. In short, electrical impulses, which are applied to one of the vagus nerves, travel to both sides of the brain, and to many disparate regions.

One vagal pathway, perhaps of particular relevance to epilepsy therapy, ascends to the forebrain via the pontine parabrachial nucleus (3). This pathway transmits sensations of visceral origin to the ventroposterior parvocellular nucleus of the thalamus, which then projects to the insular cortex (4). The parabrachial nucleus also projects to other thalamic nuclei, the amygdala, and the basal forebrain. These vagal projections travel to sites that are often found to generate seizures. One way VNS may work is through connections with the seizure generating region.

Another way in which VNS may operate is through the locus coeruleus. The locus coeruleus is another pontine nucleus that receives afferents from the NTS (5.6). While receiving less dense vagal input than the parabrachial nucleus, the locus coeruleus may be essential to the antiepileptic effect of VNS, as suggested by animal studies using ablative and immunolabeling procedures.

Vagal efferent fibers originate in the dorsal motor nucleus of the vagus and the nucleus ambiguous.

These innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and also provide parasympathetic input to the gastrointestinal viscera (2).

Because the right vagus nerve provides more innervations to the cardiac atria than the left vagus nerve (7), electrical stimulation of the left vagus nerve is generally used in clinical practice to avoid adverse cardiac effects.

THERAPEUTIC MECHANISM:

Epilepsy is defined clinically as a state of chronic recurrent seizure; the cause may be known (symptomatic epilepsy) or unknown (idiopathic or cryptogenic epilepsy). Seizure is an abnormal paroxysmal cortical cerebral activity due to hypersynchronus discharge of a group of cortical cerebral cells.

In the 1960s, studies in animals showed that repetitive vagus nerve stimulation (VNS) would either synchronize or desynchronize cortical electrical activity. The effect of stimulation on brain activity depended on the stimulus frequency and the strength of the electrical current. Because epileptic seizures are characterized by hypersynchronized

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cortical activity, the observation that VNS can desynchronize cortical rhythms suggested a potential antiepileptic effect of VNS (8-10).

VNS studies in a variety of animal models were then undertaken and have demonstrated that VNS has multiple antiepileptic properties (1-18):

- VNS can abort an ongoing seizure after seizure onset
- VNS is effective in acute seizure prophylaxis; i.e., seizure-inducing insults (e.g., strychnine administration) are less effective in inducing a seizure in the presence of VNS
- VNS is effective in chronic seizure prophylaxis, reducing seizure frequency in animal models of epilepsy
- VNS can inhibit epileptogenesis in animal models of seizure kindling

How VNS exerts its antiseizure properties exactly remains unclear.

CLINICAL APPLICATION:

In general, VNS is considered a valid treatment option for children and adults with well-documented medically-refractory seizures, who are either opposed to intracranial surgery, are not candidates, or whose medically-refractory seizures were not substantially improved by prior intracranial epilepsy surgery (19-23). Resective surgery for appropriate candidates is preferred over VNS because of the substantially greater potential for complete seizure remission

SAFETY AND TOLERABILITY:

Common side effects — side effects that occurred in at least 5 percent of patients receiving high-stimulation vagus nerve stimulation (VNS) were(66):

- Hoarseness (37 percent)
- Throat pain (11 percent)
- Coughing (7 percent)
- Shortness of breath (6 percent)

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- Tingling (6 percent)
- Muscle pain (6 percent)

Hoarseness was the only side effect that occurred significantly more often with high stimulation than with low stimulation.

Shortness of breath and pharyngitis, as well as voice alteration, occurred significantly more often in the high-stimulation group than in the low-stimulation group. Lowering the pulse width of stimulation can alleviate symptoms and allow for higher stimulation intensities. Lowering the frequency can also attenuate side effects related to VNS stimulation (26).

Cardiac events — Physiologic studies have generally found no clinically relevant effects of chronic VNS on cardiorespiratory function (28-30). However, bradycardia followed by transient asystole lasting up to 45 seconds has been reported in association with the lead test conducted during VNS implantation (the initial lead test, which is performed in the operating room when the VNS is being implanted for the first time) in approximately 0.1 percent of cases (31-33). Complete heart block due to atrioventricular nodal block was documented in three patients with no reported adverse effects (34). In some cases, a rechallenge stimulus is uneventful, and the VNS has been implanted successfully without adverse consequences. More often, the procedure is aborted. In general, baseline cardiac conduction disorders are considered a contraindication to VNS.
Two case reports describe VNS-induced episodes of bradycardia and asystole occurring 2 and 9 years after device implantation (35-36).

Other adverse effects

- Surgical complications,
- Electrode failure and lead fracture (37-40).
- Infection of the subcutaneous pocket that holds the VNS generator, usually with Staphylococcus aureus (24, 41-43),
- Sleep apnea is a relative contraindication for VNS (44-46). VNS is associated with more frequent apnea and hypopnea episodes in sleep, but this appears clinically relevant only in those with preexisting sleep apnea.
- Unilateral vocal cord paralysis occurs in about 1 percent of cases, and is attributed to intraoperative manipulation of the recurrent laryngeal nerve]. Most of these recover (24, 25, 27).
- Other cranial nerve palsies that can complicate VNS implant include Horner's syndrome and facial paralysis (47).

- Pneumothorax has been described in at least one patient (24).
- Some patients experience uncomfortable spasm of the left chest wall, which has been demonstrated to be due to collateral spread of stimulation to phrenic nerve, causing contraction of the left hemidiaphragm.
- Contraction of the left anterior sternocleidomastoid muscle may also occur as a result of current stimulating adjacent structures (48). These symptoms are often precipitated by assumption of certain postures or movement and are relieved by changing position.
- While gastrointestinal side effects might be expected with VNS, reports of this are infrequent.
- Forced normalization refers to a phenomenon of psychiatric disturbances that emerge in some patients with long-standing, high-frequency seizures when their seizures are dramatically reduced (49-50).

PATIENTS AND METHODS:

This study was conducted at Neurosciences hospital in Baghdad, between September 2008 and March 2010 .ECG traces were recorded for 32 pharmacoresistance epileptic patients only 24 traces were selected for the examination, other traces were excluded because of artifacts in ECG trace. Simultaneous 12 lead ECG were recorded for 24 pharmacoresistance epileptic patients with a mean age 21.4 + 4.4 (14 males and 10 females), just before and after implantation of the Vagal nerve stimulation device. The approval of the informed consent was obtained by all patients.

Each printed 12-leads ECG paper was scanned and the resulted image fed to the computer and was edited by "paint " program which runs under "windows" operating system .The QT,QTp and TpTe intervals were then manually measured .In each lead , the QT , QTp and TpTe intervals were the mean of two successive individual intervals at least 10 of the 12 leads was measured .The RR interval used for QT ,QTp and TpTe rate correction was the mean of the two RR intervals of the measured leads . The measured QT,QTp and TpTe intervals were corrected for the subjects heart rate by using the standard Bazett's formula (Mean QT, QTp or TpTe interval/square root of the mean RR interval).The QT dispersion was defined as the differences between the maximum and minimum QT interval duration in any of the leads measured.

Likewise, the dispersion of the QTp and TpTe intervals were determined by measuring the difference between the longest and shortest values of the QTp and TpTe intervals in each leads.

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Statistical analysis:

All statistical tests were achieved by using Microsoft Excel statistical package which run under window operating system. Data were expressed as mean + SD. Differences between group means were analyzed using unpaired t – test. A p – value < 0.05 was considered significant

RESULTS:

Table 1 shows that there are no significant differences in QT intervals before the VNS implant (0.398 + 0.039 sec) as compared to that after the implant (0.405 +¬¬ 0.042 sec) .Similarly QTp intervals were not significantly different (0.303+ 0.034, 0.300 + 0.033 sec) before and after VNS implant respectively . Moreover corrected QT dispersion before the VNS implant was 0.097+ 0.031 sec. which is lower than that after the implant (0.104+ 0.055 sec.) although it did not reach a statistical significant level. In addition to that there are no significant differences between corrected QTp dispersion before and after the VNS implant (0.073 + 0.019 sec.) and (0.090 + 0.33 sec.) respectively. In contrast, TpTe interval before VNS implant was (0.106 + 0.029 sec) which was significantly higher (P< 0.02) than that of after the implant (0.095 + 0.032 sec), this interesting result shown clearly in figure 1.

Variable	Before implant	After implant	P value
Corrected QT intervals	0.398 ± 0.039 sec	0.405 ± 0.042 sec	NS
Corrected QTp intervals	0.303± 0.034 sec	0.300 ± 0.033 sec	NS
Corrected QT dispersion	0.097± 0.031 sec	0.104± 0.055 sec	Ns
Corrected QTp dispersion	0.073 ± 0.019 sec	0.090 ± 0.33 sec	NS

Table 1: Mean + SD values of measured variable s before and after VNS implant

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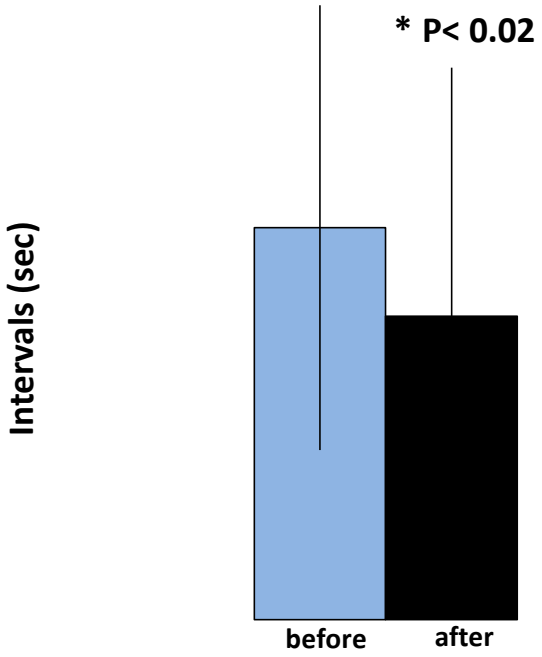

Figure 1: Corrected TpTe intervals befor and after VNS implant .

DISCUSSION:

In the present study we did not found any statistical differences in QT,QTp and TpTe intervals between male and female epileptic patients , therefore we pooled all the data together which is in controversy with MacFarlane et al and Chauhan et al they reported that the QT and QTp corrected interval of female healthy subject is significantly higher than male subject(12,13) Furthermore ,no significant gender differences were observed regarding both QT and QTp dispersion which in agreement with MacFarlane et al who proposed that QT dispersion is affected by large number of factors , however it is not influenced by age or sex (12).

Although, no statistical differences were reported in QT and QTp interval before and after the VNS implant, we focused on the interesting result revealed by the current study

which was the significant decrement in TpTe interval after VNS implant (0.095 + 0.032 sec.) as compared to that before the implant (0.106 + 0.029 sec.) with P value less than 0.02 ($P<0.02$). From the above mentioned results it looks that TpTe interval behaved differently from that of QT and QTp intervals. In view of the fact that TpTe by itself reflects the transmural dispersion of repolarization (difference in action potential duration between mid_myocardial M_cell, epicordial and endocardial cells)(14), the aforementioned results indicate that VNS implant may alter the action potential duration with its possible consequences of ventricular arrhythmia . Moreover , as there was no previous reports concerning such correlation (between VNS implant and QT,QTp and TpTe intervals) we believe that further studies are needed to assess and predict the possible hidden arrhythmogenesis risk of VNS implant .

In the current study although the corrected QT dispersion before the VNS implant (0.097+ 0.031 sec.) was lower than that after the implant (0.104 + 0.55 sec.) but it did not reach a significant value , Since QT dispersion represent the heterogeneity of repolarization in the cardiac muscle and linked to ventricular arrhythmia(15) , this increase in dispersion should be studied carefully to establish the result putting in our mind that the cutoff point of QT dispersion is 0.120 second above this value usually associated with the risk of arrhythmia(16) . Furthermore, the QTp dispersion after VNS implant (0.090 + 0.033 sec.) was also higher than before the implant (0.073 + 0.019), again it did not reach a significant value, which could be inforce the fact that VNS therapy preferentially affects myelinated fibers. This explains effects on vocalization (hoarseness) during VNS therapy, and partly explains the almost complete absence of effects on the heart and other visceral organs during VNS therapy (3).

CONCLUSION:

There is some evidence that VNS therapy may alter the electrical activity of the heart during late ventricular repolarization.

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Tofiq Journal of Medical Sciences (TJMS)

ISSN: 2377-2808

Vol.(1).No.1 ,2o14

Issued by :

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